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COLLECTED ABSTRACTS

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1945 - 1963

<u>Date</u>	<u>Author(s) and Title</u>
1945	Eisenman, A. J.: The forms and amount of morphine excreted in relation to size of dose. Fed. Proc. <u>4</u> : (1) 88 (Mar.) 1945.
	Wikler, A.: Effects of morphine on responses of nictitating membrane of cat. Fed. Proc. <u>4</u> : (1) 140-141 (Mar.) 1945.
	Wikler, A.: Effects of morphine on somatic motor components of "sham rage" in chronic decorticate cats and dogs. Fed. Proc. <u>4</u> : (1) 141 (Mar.) 1945.
	Wikler, A.: Hindlimb reflexes in chronic spinal dogs during a cycle of morphine addiction. Fed. Proc. <u>4</u> : (1) 141 (Mar.) 1945.
	Wikler, A. and Lloyd, B. J., Jr.: Effect of smoking marihuana cigarettes on cortical electrical activity. Fed. Proc. <u>4</u> : (1) 141-142 (Mar.) 1945.

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1946

Eisenman, A. J.:

Effect of morphine on the oxygen saturation of arterial blood.

Fed. Proc. 5: (1) 132 (Mar.) 1946.

Wikler, A.:

Reactions of chronic totally decorticated dogs during a cycle of morphine addiction.

Fed. Proc. 5: (1) 212-213 (Mar.) 1946.

Wikler, A.:

Effects of a cycle of morphine addiction on conditioned responses and experimental neuroses in dogs.

Fed. Proc. 5: (1) 213 (Mar.) 1946.

1947

Isbell, H., Eisenman, A. J., Wikler, A., Daingerfield, M., and Frank, K.:

Experimental addiction to 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3) in man.

Fed. Proc. 6: (1) 264 (Mar.) 1947.

Isbell, H., Eisenman, A. J., Wikler, A., Daingerfield, M., and Frank, K.:

Treatment of the morphine abstinence syndrome with 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3).

Fed. Proc. 6: (1) 340 (Mar.) 1947.

Isbell, H., Wikler, A., Eisenman, A. J. and Frank, K.:

Effects of single doses of 10820 (4-4-diphenyl-

6-dimethylamino-heptanone-3) on man.

Fed. Proc. 6: (1) 341 (Mar.) 1947.

Wikler, A., Frank, K. and Eisenman, A. J.:

Effect of single doses of 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3) on the nervous system of dogs and cats.

Fed. Proc. 6: (1) 384 (Mar.) 1947.

Wikler, A. and Frank, K.:

Tolerance and physical dependence in intact and chronic spinal dogs during addiction to 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3).

Fed. Proc. 6: (1) 384 (Mar.) 1947.

- 1948 Isbell, H. and Eisenman, A. J.:
Physical dependence liability of drugs of the methadon series, and of 6-methyl-dihydromorphine.
Fed. Proc. 7: (1) 162 (Mar.) 1948.
- Wikler, A.:
Reactions of chronic decorticated dogs during a cycle of addiction to methadone.
Fed. Proc. 7: (1) 265 (Mar.) 1948.
- Wikler, A. and Frank, K.:
Effects of electroshock convulsions on chronic decorticated cats.
Fed. Proc. 7: (1) 265-266 (Mar.) 1948.
- 1949 None
- 1950 Essig, C. F. and Marshall, W. H.:
Spreading cortical depression.
Fed. Proc. 9: (1) 38 (Mar.) 1950.
- Fraser, H. F., Flanary, H. G., Houde, R. W., and Isbell, H.:
Addiction liabilities of some drugs of the morphine series.
Fed. Proc. 9: (1) 277 (Mar.) 1950.
- Essig, C. F. and Marshall, W. H.:
The relation of electrolyte and water transfer across the arachnoid membrane to spreading cortical depression of Leao.
Electroenceph. clin. Neurophysiol. 2: (3) 360 (Aug.) 1950.
- Isbell, H., Altschul, S., Kornetsky, C. H.,
Fraser, H. F., Flanary, H. G., Eisenman, A. J.,
Wikler, A. and Hill, H. E.:
Experimental addiction to barbiturates (motion picture).
Fed. Proc. 9: (1) 701 (Mar.) 1950.

1951

Fraser, H. F. and Isbell, H.:

Addiction potentialities of isomers of 6-dimethyl-amino-4-4-diphenyl-3-acetoxy-heptane (Acetyl-methadol).

J. Pharmacol. exp. Ther. 101: (1) 12 (Jan.) 1951.

Hill, H. E., Kornetsky, C. H., Flanary, H. G., and Wikler, A.:

Studies on anxiety produced by anticipation of pain. I. Effects of morphine. (Preliminary report). J. Pharmacol. exp. Ther. 101: (1) 17 (Jan.) 1951.

Houde, R. W., Wikler, A. and Irwin, S.:

Comparative effects of morphine, mephenesin and thiopental on skin twitch and hindlimb reflexes in spinal dogs.

J. Pharmacol. exp. Ther. 101: (1) 18 (Jan.) 1951.

Houde, R. W., Wikler, A. and Irwin, S.:

Comparative actions of analgesic, hypnotic and paralytic agents on hindlimb reflexes in spinal dogs.

J. Pharmacol. exp. Ther. 101: (1) 18 (Jan.) 1951.

Wikler, A.:

Alpha rhythm and sleep patterns in the electroencephalograms of patients after frontal lobotomy.

Electroenceph. clin. Neurophysiol. 3: (1) 101 (Feb.) 1951.

Essig, C. F. and Marshall, W. H.:

Action of acetylcholine on cerebral cortex of cats and monkeys.

Fed. Proc. 10: (1) 40 (Mar.) 1951.

Eisenman, A. J.:

Effect of addiction to morphine on the excretion of water and electrolytes.

Fed. Proc. 10: (1) 180 (Mar.) 1951.

Fraser, H. F., Isbell, H., Wikler, A., Eisenman, A.J. and Kornetsky, C. H.:

Cortisone therapy in barbiturate abstinence syndrome.

Fed. Proc. 10: (1) Part I, 297 (Mar.) 1951.

- 1951 (Cont.) Hill, H. E., Kornetsky, C. H., Flanary, H. G. and Wikler, A.:
A preliminary study of the effects of anxiety and morphine on discrimination of painful stimuli.
Fed. Proc. 10: (1) 309 (Mar.) 1951.
- Wikler, A.:
The effects of large doses of N-allylnormorphine on man.
Fed. Proc. 10: (1) 345 (Mar.) 1951.
- Fraser, H. F. and Isbell, H.:
Comparative effects of morphine on former morphine addicts and nonaddicts.
Fall Meet., Am. Soc. Pharmacol. exp. Ther., Oct. 1951 (Mimeographed report).
- Isbell, H. and Fraser, H. F.:
Human pharmacology and addiction liability of derivatives of 3-hydroxy-N-methylmorphinan.
J. Pharmacol. exp. Ther. 103: (4) 348 (Dec.) 1951.
- Essig, C. F., Marshall, W. H. and Witkin, L. B.:
Components of striate reactions.
Am. J. Physiol. 167: (3) 782 (Dec.) 1951.
- 1952 Essig, C. F. and Barnard, G. L.:
Recording seizure occurrence in experimental epilepsy.
Fed. Proc. 11: (1) 44 (Mar.) 1952.
- Eisenman, A. J., Sloan, J. W. and Fraser, H. F.:
Blood nonprotein-nitrogen constituents during barbiturate addiction and withdrawal.
Fed. Proc. 11: (1) 206 (Mar.) 1952.
- Fraser, H. F., Wikler, A., Eisenman, A. J., and Isbell, H.:
N-allylnormorphine in treatment of methadone poisoning in man: Report of two cases.
Fed. Proc. 11: (1) 346 (Mar.) 1952.

- 1952 Wikler, A. and Carter, R. L.:
(Cont.) Effects of morphine and N-allylnormorphine on reflexes in dog and cat.
Fed. Proc. 11: (1) 402 (Mar.) 1952.
- Wikler, A., Carter, R. L., Fraser, H. F., and Isbell, H.:
Precipitation of "abstinence syndromes" by single doses of N-allylnormorphine in addicts.
Fed. Proc. 11: (1) 402 (Mar.) 1952.
- Fraser, H. F., Shaver, M. R., Maxwell, E. S., Isbell, H. and Wikler, A.:
Fatal termination of barbiturate abstinence syndrome in man.
J. Pharmacol. exp. Ther. 106: (4) 387 (Dec.) 1952.
- 1953 Eisenman, A. J., Isbell, H., Fraser, H. F., and Sloan, J.:
17-Ketosteroid excretion in a cycle of morphine addiction and withdrawal.
Fed. Proc. 12: (1) 200 (Mar.) 1953.
- Fraser, H. F., Isbell, H., Wikler, A., and Pescor, F. T.:
Chronic barbiturate intoxication.
Fed. Proc. 12: (1) 322 (Mar.) 1953.
- Isbell, H., Fraser, H. F., and Wikler, A.:
Addiction liability of dithienylbutylamines.
Fed. Proc. 12: (1) 333 (Mar.) 1953.
- Martin, W. R., Vernier, V. G. and Unna, K. R.:
Effect of stimulation of the reticular activating system on electrically induced cortical after-discharge.
Epilepsia 2: 145, 1953.

1954

Fraser, H. F., Isbell, H., Van Horn, G. D., and Nash, T. L.:

Use of measurement of miotic effects in evaluating analgesic drugs in man.

J. Pharmacol. exp. Ther. 110: (1) 19 (Jan.) 1954.

Martin, W. R., Vernier, V. G. and Unna, K. R.:

Effect of dilantin and phenobarbital on the response of the cortex to stimulation of activating center.

J. Pharmacol. exp. Ther. 110: (1) 35 (Jan.) 1954.

Eisenman, A. J., Fraser, H. F., and Isbell, H.:

Effects of ACTH and gonadotropin during a cycle of morphine addiction.

Fed. Proc. 13: (1) 203 (Mar.) 1954.

Carter, R. L., Fraser, H. F., and Eisenman, A. J.:

Electrophoresis blood serum protein patterns of narcotic addicts and controls.

Fed. Proc. 13: (1) 341 (Mar.) 1954.

Carter, R. L. and Wikler, A.:

Use of N-allylnormorphine in early demonstration of physical dependence on potent analgesics in dogs.

Fed. Proc. 13: (1) 342 (Mar.) 1954.

Fraser, H. F. and Isbell, H.:

Chronic intoxication of dogs with sodium barbital (motion picture).

Fed. Proc. 13: (1) 355 (Mar.) 1954.

Isbell, H. and Fraser, H. F.:

Addictive properties of methadone derivatives.

Fed. Proc. 13: (1) 369 (Mar.) 1954.

Isbell, H., Fraser, H. F., Wikler, A., Eisenman, A. J. Belleville, R. E. and Nash, T. L.:

Experimental chronic alcoholic intoxication (motion picture).

Fed. Proc. 13: (1) 370 (Mar.) 1954.

- 1954 Wikler, A., Hill, H. E., and Belleville, R. E.:
(Cont.) Effects of morphine on electric shock-conditioned inhibition of acquired feeding behavior in rats.
Fed. Proc. 13: (1) 417 (Mar.) 1954.
- Hill, H. E., Belleville, R. E. and Wikler, A.:
Anxiety reduction as a measure of the analgesic effectiveness of drugs.
Science 120: (3108) 153 (July 23) 1954.
- Wikler, A. and Pescor, F. T.:
Clinical and electroencephalographic effects of drugs in man and dog (demonstration).
Trans. Am. Neurol. Ass. Richmond, Va., 1954,
pp. 170-173.
- 1955 Fraser, H. F. and Isbell, H.:
Addictive properties of morphine derivatives.
J. Pharmacol. exp. Ther. 113: (1) 21 (Jan.) 1955.
- Isbell, H. and Fraser, H. F.:
Addiction liability of 4-4-diphenyl-6-dimethyl-amino-hexanone-3.
J. Pharmacol. exp. Ther. 113: (1) 29-50 (Jan.) 1955.
- Carter, R. L. and Wikler, A.:
Chronic meperidine intoxication in intact and chronic spinal dogs.
Fed. Proc. 14: (1) 325 (Mar.) 1955.
- Fraser, H. F. and Isbell, H.:
Morphine antagonists.
Fed. Proc. 14: (1) 340 (Mar.) 1955.
- Isbell, H., Fraser, H. F., Wikler, A. and Belleville, R. E.:
Tolerance to diethylamide of lysergic acid (LSD-25).
Fed. Proc. 14: (1) 354 (Mar.) 1955.
- Isbell, H.:
Withdrawal symptoms in "primary" meperidine addicts.
Fed. Proc. 14: (1) 354 (Mar.) 1955.

1956

Fraser, H. F. and Isbell, H.:

Chlorpromazine and reserpine: (A) Effects of each, and of combinations of each with morphine, (B) Failure of each in treatment of acute abstinence from morphine.

J. Pharmacol. exp. Ther. 116: (1) 21 (Jan.) 1956.

Martin, W. R. and Riehl, J. L.:

Quantitative comparison of the effects of chlorpromazine and pentobarbital on some autonomic responses.

J. Pharmacol. exp. Ther. 116: (1) 41-42 (Jan.) 1956.

Essig, C. F. and Wikler, A.:

Prevention of barbiturate withdrawal convulsions in cats by cerebral electrostimulation.

Fed. Proc. 15: (1) 59 (Mar.) 1956.

DeMaar, E. W. J. and Martin, W. R.:

Effects of chlorpromazine on the EEG and its activation.

Fed. Proc. 15: (1) 416 (Mar.) 1956.

Fraser, H. F., Isbell, H., Wikler, A., Belleville, R. E., Essig, C. F. and Hill, H. E.:

Minimum dose of barbiturates required to produce physical dependence.

Fed. Proc. 15: (1) 423 (Mar.) 1956.

Fraser, H. F.:

Addictive potentialities of hexamethyleneimines.

Fed. Proc. 15: (1) 423 (Mar.) 1956.

Isbell, H.:

Attempted addiction to nalorphine.

Fed. Proc. 15: (1) 442 (Mar.) 1956.

Isbell, H.:

Effect of chlorpromazine, reserpine and "frenquel" on the LSD reaction.

Fed. Proc. 15: (1) 442 (Mar.) 1956.

Martin, W. R.:

Effect of chlorpromazine on cardiovascular responses to epinephrine and norepinephrine in the cat.

Fed. Proc. 15: (1) 456 (Mar.) 1956.

- 1956 Isbell, H.:
(Cont.) The search for a nonaddicting analgesic.
Bull. Narcot. 8: (4) 5 (Oct-Dec.) 1956.
- DeMaar, E. W. J., Martin, W. R. and Unna, K. R.:
The effects of chlorpromazine on spontaneous and
evoked action potentials of the cortex and bulbar
reticular formation.
20th Internat. Physiol. Congress, 1956.
- 1957 Busch, H., Martin, W. R., Nyhan, W. L.,
Zaratzian, V. L. and Olle, E. W.:
Induction of parasympathomimetic activity of
B-substitution of pyruvic acid.
J. Pharmacol. exp. Ther. 119: (2) 136-137 (Feb.)
1957.
- Fraser, H. F., Isbell, H., Wikler, A., and
Eisenman, A. J.:
Substitution of alcohol for barbiturates in
chronically intoxicated persons.
J. Pharmacol. exp. Ther. 119: (2) 146 (Feb.) 1957.
- Martin, W. R., Busch, H., Nyhan, W. L., and
Abdulian, D. H.:
Peripheral autonomic and central nervous system
effects produced by halogenated pyruvic acids.
J. Pharmacol. exp. Ther. 119: (2) 165 (Feb.) 1957.
- Eisenman, A. J., Fraser, H. F. and Brooks, J. W.:
Plasma and urinary corticoids during a cycle of
morphine addiction.
Fed. Proc. 16: (1) 177 (Mar.) 1957.
- Abdulian, D., Martin, W. R., and Unna, K. R.:
Effects of interneuron depressants on inhibition
and facilitation of the patellar reflex.
Fed. Proc. 16: (1) 277 (Mar.) 1957.
- Fraser, H. F., Eisenman, A. J. and Brooks, J. W.:
Urinary excretion of 5HIAA and corticoids after
morphine, meperidine, nalorphine, reserpine and
chlorpromazine.
Fed. Proc. 16: (1) 298 (Mar.) 1957.

1958

Busch, H., Nair, P. V., Frank, M. I. and Martin, W. R.:

Comparative cholinomimetic effects of mono-, di-, and tri-substituted pyruvic acids.

J. Pharmacol. exp. Ther. 122: (1) 9a (Jan.) 1958.

Fraser, H. F., Isbell, H., Wikler, A., Eisenman, A. J. and Van Horn, G. D.:

Studies of normorphine in man.

J. Pharmacol. exp. Ther. 122: (1) 22a (Jan.) 1958.

Kniazuk, M., Martin, W. R. and Unna, K. R.:

A new method of measuring movement in small animals.

J. Pharmacol. exp. Ther. 122: (1) 58a (Jan.) 1958.

Martin, W. R., Longo, V. G. and Unna, K. R.:

Effect of mephenesin on Renshaw cells.

J. Pharmacol. exp. Ther. 122: (1) 49a (Jan.) 1958.

Belleville, R. E., Pescor, F. T., Hill, H. E. and Wikler, A.:

Effects of analgesic doses of methadone, meperidine, and morphine on pain conditioned inhibition of lever pressing in rats.

Fed. Proc. 17: (1) 548 (Mar.) 1958.

Fraser, H. F., Isbell, H. and Van Horn, G. D.:

Norcodeine in man.

Fed. Proc. 17: (1) 567 (Mar.) 1958.

Martin, W. R. and Eades, C. G.:

Effect of various central depressants on pressor response evoked by stimulation of the mesencephalon. Program, Fall Meet., Am. Soc. Pharmacol. exp. Ther., Ann Arbor, Mich. (Aug.) 1958, p. 25.

Sloan, J., Eisenman, A. J., Fraser, H. F., and Isbell, H.:

Preliminary observations of the urinary excretion of normorphine and morphine in man.

Program, Fall Meet., Am. Soc. Pharmacol. exp. Ther., Ann Arbor, Mich. (Aug.) 1958, p. 51.

- 1959 Fraser, H. F. and Isbell, H.:
 Pharmacology and addiction liability of dL- and
 d-propoxyphene (Darvon).
 Pharmacologist 1: (2) 78 (Aug-Sept.) 1959.
- 1960 Martin, W. R. and Fraser, H. F.:
 A comparison of the addiction liability of
 intravenously administered heroin and morphine
 in man.
 Pharmacologist 2: (2) 97 (Fall) 1960.
- Fraser, H. F., Van Horn, G. D., Martin, W. R. and
Isbell, H.:
 New methods for evaluating addiction liability of
 morphine-like drugs.
 Pharmacologist 2: (2) 97 (Fall) 1960.
- Wikler, A., Green, P. C., Smith, H. D. and
Pescor, F. T.:
 Use of a benzimidazole derivative with potent
 morphine-like properties orally as a presumptive
 reinforcer in conditioning of drug-seeking
 behavior in rats.
 Fed. Proc. 19: (1) 22 (Mar.) 1960.
- Essig, C. F. and Flanary, H. G.:
 Progressive increase of electroshock convulsive
 threshold in cats.
 Fed. Proc. 19: (1) 281 (Mar.) 1960.
- 1961 Fraser, H. F., Martin, W. R., Wolbach, A. B., and
Isbell, H.:
 Addiction liability of 1-(p-chlorphenethyl)-2-
 methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline
 HCl.
 Fed. Proc. 20: (1) Part I, 310 (Mar.) 1961.
- Martin, W. R., and Eades, C. G.:
 Demonstration of acute tolerance and physical
 dependence in the dog.
 Fed. Proc. 20: (1) Part I, 310 (Mar.) 1961.
- Eisenman, A. J. and Martin, W. R.:
 Effect of morphine and nalorphine on serum CO₂,
 serum pH and respiratory rate in the decerebrate
 cat.
 Fed. Proc. 20: (1) Part I, 310 (Mar.) 1961.

1962

- Sloan, J., Eisenman, A. J., Brooks, J. W., and Martin, W. R.:
Catecholamine and serotonin levels in tissues of morphine addicted rats following abrupt withdrawal.
Fed. Proc. 21: (2) 326 (Mar-Apr.) 1962.
- Martin, W. R., Fraser, H. F. and Isbell, H.:
A comparison of the effects of intramuscularly administered pentobarbital sodium and morphine sulfate in man.
Fed. Proc. 21: (2) 326 (Mar-Apr.) 1962.
- Jones, B. E., Martin, W. R., Isbell, H. and Fraser, H. F.:
Evaluation of a photographic method of estimating pupil diameter in man.
Fed. Proc. 21: (2) 326 (Mar-Apr.) 1962.
- Isbell, H., Wolbach, A. B. and Rosenberg, D. E.:
Observations on direct and cross tolerance with LSD and dextroamphetamine in man.
Fed. Proc. 21: (2) 416 (Mar-Apr.) 1962.
- Fraser, H. F., Jones, B. E., Rosenberg, D. E. and Thompson, A. K.:
Effects of addiction to i.v. heroin as compared to placebo on patterns of activity.
Pharmacologist 4: (2) 154 (Fall) 1962.
- Wikler, A., Martin, W. R., Pescor, F. T., and Eades, C. G.:
Factors regulating oral consumption of etonitazene solution in morphine addicted rats.
Pharmacologist 4: (2) 154 (Fall) 1962.
- Martin, W. R., Wikler, A., Eades, C. G., and Pescor, F. T.:
Tolerance and physical dependence to morphine in rats.
Pharmacologist 4: (2) 154 (Fall) 1962.

- 1963 Jones, B. E., Flanary, H. G., and Clements, T. H.:
Effects of morphine and pentobarbital on electro-
dermal activity and conditioned electrodermal
responses in man.
Pharmacologist 5: (2) 233 (Fall) 1963.
- Weil-Malherbe, H., Smith, E. R. B., Eisenman, A. J.,
and Fraser, H. F.:
Urinary excretion of catecholamines and some of
their metabolites during a course of morphine
addiction and withdrawal in two human subjects.
Fed. Proc. 22: (2) (Pt. I) 567 (Mar-Apr.) 1963.

The form and amount of morphine excreted in relation to size of dose. ANNA J. EISENMAN, Research Dept., U. S. Public Health Service Hospital, Lexington. In the preliminary experiments, increasing doses of morphine sulfate were given to human post-addicts and the first and second urine voidings were analyzed. The results indicated that, in general, free morphine does not appear in the urine before the third hour. Detectable amounts of bound morphine appeared during the first twenty minutes.

In the second set of experiments, four subjects were given 20, 30, 40 and 60 mg. of morphine sulfate at fortnightly intervals. Urine was collected at one hour, at three or five hours, and at 24 hours. Since the three hour specimens after the 20 and 30 mg. doses failed to show free morphine, the second collection interval for the 40 and 60 mg. experiments was set at five hours. Three hour values exceeded the 0.5 mg. allowed for a blank but the results are the sum of two analyses neither of which exceeded 0.5 mg. About 2 mg. of free morphine was excreted after five hours. For the 24 hour specimens the amount of free morphine bears no constant relation to the total amount excreted or to the dose of morphine. The ratios of total morphine to dosage vary inversely as the dosage, e. g., 65 per cent for 20 mg. vs. 43 per cent for 60 mg. This may explain why a 60 mg. dose of morphine is not three times as effective as a 20 mg. dose. There is a slight decrease in urine volume with increasing amounts of morphine.

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Effects of morphine on responses of the nictitating membrane of the cat. ABRAHAM WIKLER.¹
Research Dept. U. S. Public Health Service
Hospital, Lexington, Ky. The neural pathways
traversed by the sciatic nerve—nictitating membrane (N. M.) reflex of the cat have been elucidated by Morison and Rioch (Am. J. Physiol. 120: 257, 1937). In the present study, the action of morphine on this reflex has been investigated by the use of similar techniques. Sixteen cats were used, usually after anesthetizing with urethane, 1.0 to 1.5 gm./kg. I. V., although some were previously decorticated and studied after "curarization" with β -erythroidin under artificial respiration. The adrenal glands were ligated in some experiments but this did not alter the results. The responses of the N. M. were recorded kymographically. All stimulation was effected by use of a voltage regulated 60 cycle source of electric current. In some experiments, blood pressure was also recorded from a femoral artery after intravenous injection of Pontamine Fast Pink.

Marked diminution of the amplitude of the response of the N. M. to sciatic nerve stimulation regularly followed subcutaneous injection of morphine, 5-40 mg/kg. This was true even when morphine caused some spontaneous contraction of the N. M. and it was not altered by previous ablation of the cerebral cortex. Responses elicited by direct stimulation of the hypothalamus through bipolar electrodes inserted stereotactically were moderately reduced by morphine. Morphine did not depress responses of the N. M. elicited by direct stimulation of frontal cortex, and had only slight depressive effects on those evoked by stimulation of the mesencephalic tegmentum. Blood pressure responses to reflex or direct stimulation were not altered by morphine.

¹ Surgeon (Reserve) U. S. Public Health Service

Note: In "curarized" chronic decorticated cats not previously anesthetized, morphine had only a slight depressant effect on the sciatic nerve-nictitating membrane reflex; this effect was greatly enhanced by previous injection of a small amount of urethane (0.25 cc./kg.) which by itself had no effect on the reflex.

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Effects of morphine on somatic motor components of "sham rage" in chronic decorticate cats and dogs. ABRAHAM WIKLER,¹ Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. Seventeen observations on the effects of 1-15 mg/kg. of morphine were made on 5 cats, 2 to 41 days after completion of aseptic removal of the cerebral cortex, and 22 observations were made on the effects of 3-200 mg/kg. of morphine on 3 dogs, 2 to 95 days after aseptic decortication. In the cat preparations, restraint, maximal pinching of the toes or faradization of the skin evoked classical "sham rage"—tail lashing, struggling, clawing, running, extrusion of the claws, spitting, snarling and vocalization as well as various autonomic responses. All the somatic responses were greatly reduced or abolished by 2-15 mg/kg. of morphine (subcutaneous). Vocalization and extrusion of the claws were least affected. This depressive effect persisted for as long as 10 hours concurrently with spontaneous walking and running movements which appeared 1-2 hours after injection, but which were inhibited by nociceptive stimuli. Delayed convulsions followed the larger doses.

In the decorticate dogs, restraint, pinching or faradization of the skin evoked struggling, running, baring of teeth, biting, lashing of the tail and vocalization, as well as autonomic responses. The somatic responses were greatly reduced or abolished by all doses of morphine administered (subcutaneous). Vocalization was least affected. General sedation, with abolition of righting reflexes followed all doses up to 100 mg/kg. Above this dose, initial sedation was followed after 1-2 hours by spontaneous running, circling, and later, convulsions, as in decorticated cats. Similarly, nociceptive stimuli inhibited these delayed running movements but evoked no somatic sham rage responses.

¹Surgeon (Reserve) U. S. Public Health Service.

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Hindlimb reflexes in chronic spinal dogs during a cycle of morphine addiction. ABRAHAM WIKLER.¹ Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. A. Single Doses. Eighteen preliminary observations were made on the effects of single subcutaneous injections of 2-100 mg/kg. of morphine sulfate on the hindlimb reflexes of four dogs whose spinal cords had been transected aseptically at D10, 6-210 days prior to testing. In all cases, the flexor, crossed extensor, Phillipson's, and "mark time" reflexes, and "extensor tone" were depressed or abolished while the extensor thrust reflex was greatly exaggerated. When the knee jerk was a simple twitch, it was little affected by morphine; when it was sustained, it was converted into a twitch.

B. Daily Doses. Two of these preparations were subjected to three periods (26, 56 and 80 days each, of daily administration of morphine, beginning with 10 mg/kg. and gradually increasing to 100 mg/kg. At each dose level, tolerance gradually developed to the depressing effects of morphine on the flexor reflex but not to the excitant effects on the extensor thrust. The preinjection activity of all the hindlimb reflexes became hyperactive toward the end of each addiction period.

C. Withdrawal. Two to three days after abrupt cessation of injections the flexor, crossed extensor and mark-time reflexes became supernormally hyperactive, while the extensor thrust was depressed. As the hyperactivity of the flexor reflex gradually subsided, the extensor thrust became more active. The peak of the general abstinence syndrome (restlessness, vomiting, diarrhea, rhinorrhea, panting, yawning and hyperpyrexia) as well as that of the spinal reflexes occurred on the fourth day of withdrawal, but whereas the former ended after two weeks, the latter persisted for several months.

¹ Surgeon (Reserve) U. S. Public Health Service.

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Vol. 4, No. 1, March, 1945

Effect of smoking marihuana cigarettes on cortical electrical activity. ABRAHAM WIKLER¹ and BOLIVAR J. LLOYD, JR.² (by invitation). *Research Dept., U. S. Public Health Service Hospital, Lexington, Ky.* In twenty-two experiments on nineteen patients electroencephalograms were recorded from bipolar occipital leads before and after smoking 2 or 3 marihuana cigarettes. In all cases a marked increase in the number and amplitude of fast waves of the frequency of muscle potentials was observed after smoking. These were apparently of muscular, not cortical origin, since the same effects of smoking marihuana were observed in electromyograms recorded from temporalis muscle. In 4 cases the post-marihuana record could not be read satisfactorily because of the prevalence of these potentials. In the eighteen remaining cases, there was no significant change in the alpha frequency in thirteen, a significant change in the alpha frequency in thirteen, a decrease in 3, and an increase in 2. The alpha percentage was unchanged in ten and an average decrease of 19% was observed in 8.

That the augmented muscle activity was due to a central (probably cortical) action of marihuana was indicated by comparison of electrical activity in muscles of both hindlegs (one of which was denervated) with those of the temporalis muscle in spinal cats with head and brain circulation intact. Respiration was maintained artificially with an apparatus that permitted breathing of air or various mixtures of air and marihuana smoke. During breathing of a light mixture of marihuana and air the slower cortical frequencies (6-9 per second) disappeared. Concurrently, temporalis muscle activity increased. In contrast, no change was seen in the electrical activity of either group of hindleg muscles. During breathing of concentrated marihuana smoke (short of anoxia) slowing of cortical activity with concomitant decrease in muscle electrical activity was observed.

¹ Surgeon (Reserve) U. S. Public Health Service.

² Assistant Scientific Aide.

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NIMH ADDICTION RESEARCH CENTER

Reprinted from FEDERATION PROCEEDINGS

PHS, Lexington, Ky., March, 1948

Apr 15 28

Effect of morphine on the oxygen saturation of arterial blood. ANNA J. EISENMAN. Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. Twelve experiments were done on ten subjects, all former morphine addicts. Blood was collected from the femoral artery and defibrinated anaerobically and analyzed for oxygen content and capacity and in most cases for serum carbon dioxide content by means of the Van Slyke manometric apparatus. Large single doses of morphine sulfate (75 to 175 mg.) were administered. Blood was again collected at the peak of the subject's reaction, as manifested by mild narcosis, the head falling forward on the chest, talkativeness or drowsiness. This state was usually attained in about three hours after the administration of the drug. In all twelve cases, the oxygen saturation of the blood decreased from two to eighteen per cent. The oxygen capacity did not vary much from the original value; the maximum change, an increase of one volume per cent, was noted in the case of a patient who had vomited. In eight of ten cases the serum carbon dioxide content increased about three volumes per cent. This increase was not proportional to the drop in oxygen saturation. The variations were unrelated to the amounts of morphine administered but showed rough relationship to the subject's reaction as objectively observed. One individual who reacted only mildly to the maximum dose of 175 mg. sustained minimal blood changes. The striking observation from these studies is the small magnitude of the changes resulting from relatively large doses of morphine. These changes in the blood can be demonstrated only at the time of maximum reaction.



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Reprinted from FEDERATION PROCEEDINGS
Vol. 5, No. 1, March, 1946

Reactions of chronic totally decorticated dogs during a cycle of morphine addiction. ABRAHAM WIKLER. Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. The effects of morphine (1-20 mg. per kg.) were studied on general behavior, pain threshold (turning of head to opposite side on electrical AC stimulation of tooth pulp through double amalgam fillings), temperature, cardiac rate and respiration in five long-surviving totally decorticated dogs. Three of these preparations were then subjected to regular daily injections of morphine (10-20 mg. per kg. 2 to 4 times daily). One died on the 10th day of addiction while in 2, addiction was continued for 2 months after which morphine was withdrawn abruptly. Another dog was addicted to morphine for 3 months and then decorticated, following which morphine was withdrawn. *Single Doses.* Morphine regularly caused general sedation, loss of body righting reflexes, lowering of body temperature and cardiac rate and elevation of pain threshold. Respirations were variably and only slightly affected. *Addiction.* Tolerance to elevation of pain threshold by morphine developed rapidly (two weeks) as did also tolerance to general sedative effects; effects on temperature and cardiac rate changed little. Later, pre-injection temperature and cardiac rate became elevated, motor restlessness and affective irritability (barking and biting when handled) appeared, while pain threshold level remained unchanged. *Withdrawal.* Following abrupt withdrawal the preparations exhibited marked motor restlessness, elevation of temperature and cardiac rate and rhinorrhea. One dog died accidentally. In another, the signs of withdrawal subsided after 3 days, and after 1 week morphine again elevated pain threshold and caused general sedation. Addiction was resumed in the third preparation and is still maintained. The morphine "withdrawal syndrome" was reproduced by injection of eserine (0.5 mg. per kg.) in a non-addicted chronic totally decorticated dog.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 5, No. 1, March, 1946

Effects of a cycle of morphine addiction on conditioned responses and experimental neuroses in dogs. ABRAHAM WIKLER. Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. (Read by title.) Conditioned leg withdrawal responses were established in 7 dogs by pairing faradic shocks to one hind leg with pure tones of frequencies from 350 to 500 cycles per second or with a strong light. Positive and negative responses were then developed to the limit of the dogs' ability to differentiate between such signals. During the first few months of such training morphine (1 to 10 mg. per kg.) impaired differentiation markedly or abolished the conditioned response altogether. In some excitable dogs morphine (0.5 mg. per kg.) produced mild sedation and improved learning and differentiation. In all dogs the effects of morphine were temporarily abolished by noxious stimulation. As training continued single injections of morphine exerted less effect on conditioned responses and in one dog after 6 months of training morphine ceased to impair differentiation at all. Experimental neuroses were produced in 2 dogs by exhibiting negative and positive conditioned stimuli simultaneously. One neurosis was characterized by schizophrenic-like inhibition and catatonia and the other by manic-like excitement and hyperactivity. These two neurotic dogs and one very stable dog which could not be made neurotic were subjected to daily injections of morphine (10 mg. per kg. twice daily) for three months. Before tolerance appeared morphine reduced the excitability and improved performance in the manic dog, but had little effect on the performance of the other two. As tolerance developed all three dogs became increasingly restless and irritable, but this did not impair the differential responses of the stable dog. After abrupt withdrawal all dogs showed a mild, but characteristic, "abstinence syndrome" which subsided after 3 to 5 days. After this period the behavior and performance of the neurotic dogs remained unchanged while the stable dog became cooperative and friendly and continued to respond correctly to complex conditioned stimuli.



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Reprinted from FEDERAL BUREAU OF INVESTIGATION
Vol. 4, No. 1, March, 1947

Experimental addiction to 10820 4-4-diphenyl-6-dimethylamino-heptanone-3¹ in man. HARRIS ISBELL (by invitation), ANNA J. EISENMAN, ABRAHAM WINKLER (by invitation), MARY DINGENFELD (by invitation), and KARL FRANK (by invitation). Research Dept., U. S. Public Health Service Hospital, Lexington, Ky. 10820 was administered subcutaneously 4 times daily, in doses gradually increasing from 5 to 45 mg. (or 60 mg.), to 10 former morphine addicts who volunteered for the experiments. When the daily dosage reached 60 mg. narcosis, sedation, euphoria, cessation of productive activity, neglect of personal appearance, and increased irritability appeared. Increases in dosage were frequently requested. Roschach tests generally showed accentuation of the basic personality structure and decreased anxiety.

Tolerance to the following became evident as addiction progressed: analgesic, emetic, narcotic and sedative effects; diminution in alpha frequency and percentage and increase in delta frequency in the electroencephalogram; miosis; and anorexia.

Bradycardia, bradypnea, systolic hypotension, constipation, fever and weight loss were observed throughout addiction.

NPN's, cephalin-cholesterol-flocculations, blood bilirubins, red and white cell counts, hemoglobins, and urinalyses remained normal. Blood sugars were usually in the low normal range.

On the 3rd to 7th days after abrupt withdrawal the men complained of weakness and anxiety. Systolic blood pressures, temperatures and pulse rate (but not respiratory rates) were elevated above preaddiction values. Caloric intake and body weight declined slightly. Sleep was not affected. One subject vomited once; none had diarrhea. Fasting blood sugars and red and white cell counts did not change. Autonomic disturbances were minimal. The average intensity of abstinence (Himmelbach score) did not exceed 20 points. One unstable subject developed an acute panic reaction on the 4th day of withdrawal, and 3 other patients had inconsistent subjective complaints without discoverable physical basis.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 6, No. 1, March, 1947

Treatment of the morphine abstinence syndrome with 10820 (4,4-diphenyl-6-dimethylamino-heptanone-3). HARRIS ISBELL (by invitation), ANNA J. EISENMAN (by invitation), ABRAHAM WIKLER, MARY DAINGERFIELD (by invitation), and KARL FRANK (by invitation). *Research Dept., U. S. Public Health Service Hospital, Lexington, Kentucky.* 7 former addicts, who volunteered for experiments, received 4 subcutaneous injections of morphine sulfate daily for 28 to 56 days. The amount of morphine was gradually increased from 20 to 80 mg. (or 180 mg.) per dose. By the 38th hour following abrupt withdrawal of morphine all subjects showed signs of severe abstinence which disappeared in 4 hours in 4 subjects who received 2 doses of 20-45 mg. of 10820. These 4 subjects continued to receive 60-180 mg. of 10820 daily for 10-21 days during which they exhibited no signs of abstinence. 36 hours after withdrawal of morphine, the remaining 3 patients were given morphine in amounts just sufficient (240-360 mg. daily) to prevent the appearance of abstinence signs for 7 days, after which 60-100 mg. daily of 10820 was substituted. No signs of abstinence appeared during the next 14 days.

The abstinence syndromes which appeared following abrupt withdrawal of 10820 were so mild in all 7 instances that no treatment was required. The patients had no complaints for 2-3 days, but reported weakness and anxiety for 7 days thereafter. Systolic blood pressures and rectal temperatures (but not respiratory rates) were elevated slightly above preaddiction levels. Caloric intake and body weight declined slightly. Fasting blood sugar values and total and differential WBC counts were unchanged. No patients had diarrhea. Vomiting occurred rarely. Autonomic disturbances were minimal. The average intensity of the abstinence syndrome (Himmelsbach score) did not exceed 25 points. No signs of abstinence could be detected 14 days after withdrawal.

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Reprinted from *Federal Register*
Vol. 1, No. 1, March, 1947

Effect of single doses of 10820 (4,4-diphenyl-6-dimethylamino-heptanone-3) on man. HARRIS ISBELL (by invitation), ABRAHAM WILKER, ANNA J. EISENMAN (by invitation), and KIRK FRINE (by invitation). Research Dept., U. S. Public Health Service Hospital, Lexington, Kentucky. Subcutaneous doses of 2.5 mg. of 10820 elevated the pain thresholds (Hardy-Wolff technique) of both non-addict and former addict subjects as much as 10 mg. morphine sulfate. 5 mg. of 10820 had no effect on temperature, pulse, blood pressure or respiration. 10 to 30 mg. slowed the pulse rate 4 to 10 beats per minute, and depressed systolic blood pressure 5 to 10 mm. Temperatures were lower in some subjects. EKG showed only sinus bradycardia after 10-30 mg. 50-75 mg. did not affect the fasting blood sugar levels. 5 mg. produced nausea 3 times and vomiting once in 16 trials, but 30 mg. frequently produced these effects. 10 mg. or more, produced miosis which was less marked than after morphine. 30 mg. had a potent, and anti-diuretic effect which was maximum after 2 hours as contrasted to 30 minutes after morphine.

5 to 15 mg. had no effect on the electroencephalogram. In some cases, 30 mg. caused slowing of alpha frequency, diminution in alpha percentage, and increase in the delta percentage. Narcosis and sedation were not evident with 10 mg. or less, but were always produced by 30 to 30 mg. The onset of narcosis and sedation was slow as compared to morphine, but more prolonged. In former addict subjects, doses of 10 to 30 mg. regularly induced unmistakable euphoria.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 6, No. 1, March, 1947

Effects of single doses of 10820 (4-4-diphenyl-6-dimethylamino-heptanone-3) on the nervous system of dogs and cats. ABRAHAM WIKLER, KARL FRANK (by invitation) and ANNA J. EISENMAN (by invitation). Research Dept., U. S. Public Health Service Hospital, Lexington, Kentucky. In intact dogs, subcutaneous injection of 2-10 mg./kg. of 10820 caused sedation, elevation of tooth pain reaction threshold (facial twitch in response to bipolar electrical stimulation of tooth), hypothermia, bradycardia, salivation and slowing of cortical electrical activity. In conditioned reflex experiments the degree of impairment of adaptive response patterns varied inversely as their stability (predictability). Blood sugar was elevated about 30% by initial doses of 0.5 to 5.0 mg./kg. Doses of 50 mg./kg. caused convulsions, usually with spontaneous recovery.

In chronic decorticated dogs 2-5 mg./kg. caused whining, immobility, abolition of "sham rage" reactions to restraint or noxious stimulation, elevation of tooth pain reaction threshold, bradycardia and hypothermia.

In chronic spinal dogs (lower thoracic level) 2-5 mg./kg. reduced or abolished the hindlimb flexor, crossed extensor and Philipson's reflexes, augmented the extensor thrust, and altered the amplitude of the knee jerk but little.

In chronic decorticate cats, 1-5 mg./kg. caused elevation of threshold for nictitating membrane responses to nociceptive stimuli (electrical stimulation of skin through Michel clip electrodes), pyrexia, mydriasis, extensor rigidity of forelegs and delayed motor restlessness; instead of evoking "sham rage," nociceptive stimulation inhibited motor activity and augmented rigidity and opisthotonus.

In acutely decerebrated cats, effects of 2-5 mg./kg. varied with the exact level of the preparation. Extensor rigidity was slightly augmented or diminished, respiratory rate generally slowed and, in one experiment, delayed running movements appeared which ceased during application of pressure to extremities or tail.

In general, in all preparations, 10820 acted like morphine.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 6, No. 1, March, 1947

Tolerance and Physical Dependence in Intact and chronic spinal dogs during addiction to 10820 (4 - 4 - diphenyl - 6 - dimethylamino - heptanone-3). ABRAHAM WIKLER and KARL FRANK (by invitation). Research Dept., U. S. Public Health Service Hospital, Lexington, Kentucky. In intact dogs receiving subcutaneous injections of 10820 at times daily increasing gradually from 1.0 to 5.0 mg./kg. tolerance to the sedative, analgesic (tooth pain reaction threshold), and hypothermic effects of the smaller doses was evident at the end of the first week and to those of the largest dose at the end of the eighth week, when injections were discontinued abruptly. Twelve to 18 hours later, marked restlessness, tremors, muscle twitches, panting, pyrexia, mydriasis, rhinorrhea, occasional vomiting and mild diarrhea were observed. The abstinence syndrome reached a peak about the 24th hour and largely disappeared by the 48th hour. After one week tolerance was markedly reduced. The 10820 abstinence syndrome appeared to be more rapid in onset, more severe and of shorter duration than that of morphine in dogs.

In chronic spinal dogs similarly treated, partial tolerance to the effects of even 5 mg./kg. of 10820 on the hindlimb reflexes was noted at the end of the 8th week. Following abrupt withdrawal, in addition to the abstinence syndrome above the level of spinal cord transection (lower thoracic), greatly exaggerated running movements of the hindlimbs appeared, reaching a peak at the 36th hour with gradual subsidence during the next two weeks. During this period the flexor reflex was hyperactive and the extensor thrust reduced. Afterward the reflexes returned to the approximate preaddiction level. Artificially induced pyrexia failed to reproduce the hindlimb abstinence syndrome. The latter resembled strikingly the effects of eserine on the hindlimb reflexes and the changes in the latter during morphine withdrawal.





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Reprinted from FEDERATION PROCEEDINGS
Vol. 7, No. 1, March, 1948

P. 16 ✓

Physical dependence liability of drugs of the methadon series and of 6-methyldihydromorphone. HARRIS ISBELL (by invitation) and A. J. EISENMAN. Research Department, U. S. Public Health Service Hospital, Lexington, Kentucky. Average doses of 21 mgm. of racemic methadon (6-dimethylamino-4-4-diphenyl-3-heptanone), 11 mgm. of levo-methadon, 90 mgm. of dextromethadon, 84 mgm. of racemic methadol (6-dimethylamino-4-4-diphenyl-3-heptanone) 78 mgm. of racemic isomethadon (5-dimethylamino-4-4-diphenyl-3-hexanone) and 83 mgm. of 6-methyl-dihydromorphine were administered to 10 men, at the 28th to 32nd hour of abstinence from morphine. Levo-methadon and racemic methadon reduced the intensity of the abstinence more than did 30 mgm. of morphine. Dextromethadon and methadol had no effect. Isomethadon reduced the intensity of abstinence as much as did 30 mgm. of morphine. 6-Methyldihydromorphone had only a small and transient effect.

1 mgm. of levo-methadon was substituted for each 8-10 mgm. of the stabilization dose of morphine in 7 subjects who were addicted to morphine without the appearance of signs of abstinence. Following withdrawal of the levo-methadon after 14 days substitution, a definite abstinence syndrome ensued, which was similar to the syndrome seen after withdrawal of racemic methadon. Following the substitution of 1 mgm. of isomethadon for each 1.5 mgm. of the stabilization dose of morphine, signs of mild abstinence appeared in 2 of 5 cases. When the isomethadon was withdrawn after 14 days substitution, an abstinence syndrome, very similar to the morphine abstinence syndrome, became evident 12 hours after the last dose was administered.

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Made in United States of America

Reprinted from *Experientia* PROCEEDINGS
Vol. 7, No. 1, March, 1943

Reactions of chronic decorticated dogs during a cycle of addiction to methadon. ABRAHAM WIKLER. Research Department, U. S. Public Health Service Hospital, Lexington, Kentucky. In 2 chronic decorticated dogs subcutaneous injection of 2.0 to 5.0 mg./kg. of methadon ("amidone", "10820") regularly reduced spontaneous activity, depressed sham rage responses to pinching or restraint, elevated tooth pain reaction threshold, lowered body temperature and cardiac rate. In one such preparation, 43 days after completion of decortication, methadon was injected subcutaneously every 6 hours for 60 days, the dose being increased rapidly from 2.0 to 5.0 mg./kg. A high degree of tolerance developed to the analgesic, sham rage depressant and temperature lowering effects, but tolerance to the depressant effects on spontaneous activity was less marked. As addiction progressed pre-injection restlessness and hyperirritability were observed. Two attempts at abrupt withdrawal were abandoned because the preparation exhibited extreme restlessness, marked loss of irritability, profuse salivation, vomiting, tachycardia, fever, weak pulse and gasping respirations. After a 2-day withdrawal, restlessness, hypoiritability, persistent rooting and gnawing at the floor of the circular cage were exhibited for about two weeks after which there was a gradual return to the preaddiction state. In another preparation, 6 months after completion of decortication, methadon 2.0 mg./kg. was substituted for morphine after tolerance to the latter had been established. This dose was injected subcutaneously every 6 hours for 34 days. Partial cross tolerance to morphine was observed. On abrupt withdrawal of methadon, an abstinence syndrome was observed which was milder but qualitatively the same as that described above. The methadon abstinence syndrome in both preparations was indistinguishable from that of morphine.



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Reprinted from FEDERATION PROCEEDINGS
Vol. 7, No. 1, March, 1948

Effects of electroshock convulsions on chronic decorticated cats. ABRAHAM WIELER and KARL FRANK (by invitation). Research Department, U. S. Public Health Service Hospital, Lexington, Kentucky. In chronic decorticated cats convulsions were induced by passage of 200-450 milliamperes of 60 cycle A.C. from vertex to palate. Immediately after each seizure and for $\frac{1}{2}$ to 4 hours afterward sham rage responses (chiefly facio-vocal) to pressure-pain stimuli applied to the tail were markedly reduced while other sham rage responses (springing, clawing, lashing of tail) evoked by non-nociceptive stimuli were unaffected or enhanced. In 3 of the preparations licking responses to tactile stimulation of the perineal region were temporarily depressed after each seizure. Righting reflexes returned within a few minutes after each convolution while pulse rate and rectal temperatures were not altered significantly. Apnea occurred during the seizures and was followed by transient hyperventilation. No cumulative or new effects were observed after daily electroshock convulsions for 5 to 9 days. In terminal experiments the preparations were curarized and maintained on artificial respiration. Electrical activity was recorded from vertex and sphenoid screw leads immediately after electroshock induced as above. The electroencephalographic patterns were characterized by bursts of 6-21 per second rhythms interrupted by silent intervals finally terminating after a more prolonged 15-18 per second rhythm. In places fast and slow wave sequences were seen. This was more marked in preparations which were morphinized prior to electroshock. Neuropathologic studies of the remaining brains revealed no residual neocortex. The microscopic changes did not differ in degree or kind from those seen in other chronic decorticated cats which were not subjected to electroshock convulsions.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 9, No. 1, March, 1960

Spreading cortical depression. CARL F. EDEG^{*}
AND WADE H. MARSHALL. Intramural Research
Branch, National Inst. of Mental Health and Lab.
of Physical Biology, Exper. Biology and Medicine
Inst., National Inst. of Health, Bethesda, Md.

A cat or monkey preparation of exposed cortex maintained under physiological conditions rarely produces spreading depressions. We have developed 3 almost certain methods of producing the reaction: 1) radical internal dehydration; 2) cooling the surface of the cortex approximately 10°C.; and 3) exposure to room air for several hours. A 4th but uncertain method is some unknown traumatic factor in surgical procedure. An occasional monkey preparation will yield the reaction within the 1st hour after exposure to room air. Failures of reactions are correlated with highly negative cortical base line voltages. The chilled cortex (monkey) shows 4 definite components: D1, D2, D3, and D4. D1 jumps the central sulcus, D2 follows the cortex or pia membrane. D1 and D2 velocities are approximately 0.08 mm/sec. D3 velocity is about 0.0053 mm/sec., and D4 velocity is about 0.0035 mm/sec. The D1, D2, and D3 reactions are obtained after prolonged exposure to room air but at 1.5-3 times the above velocities. In both cooled and room air exposed preparation D4 is not always seen. The reactions develop gradually to the same pattern that can be obtained in 10 minutes by cooling the cortex. The initial stages of development of the phenomena can be seen within 15 minutes after exposure to room air.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 9, No. 1, March, 1960

Addiction liabilities of some drugs in the morphine series. H. F. FRASER,* H. G. FLANARY,* R. W. HOUTDE* and HARRIS ISBELL. Research Division, USPHS Hospital, Lexington, Ky.

The addiction liabilities of dihydrocodeinone (dicodide), 6-methyldihydromorphine ('6-methyl'), and 3-hydroxy-N-methyl morphinan (morphinan) were tested in former morphine addicts, by the single dose method for the detection of euphoria (all compounds), the single dose method for relief of abstinence from morphine (dicodide and '6-methyl') and by direct addiction (all compounds). Thirty mg. of dicodide and 6-methyl or 10-15 mg. of morphinan subcutaneously or intravenously induced morphine-like euphoria in these subjects. Forty-five mg. of dicodide administered subcutaneously at the 30th hour of abstinence from morphine relieved withdrawal symptoms almost completely. Ninety mg. and 120 mg. of '6-methyl' administered at the 28th and 32nd hours of abstinence produced subjective relief but had only minor effects on objective signs. Five volunteers received the drugs for 32-38 days. The maximum daily dosages attained were 240, 180, and 60 mg. for dicodide, '6-methyl' and morphinan respectively. During the experiment, behavior of the men addicted to the 3rd drugs resembled that of men addicted to morphine. Complete tolerance to the sedative action was not attained. The electroencephalograms of subjects receiving dicodide and morphinan were slowed throughout addiction. The pain thresholds (modified Hardy-Wolff-Goodel) of men receiving '6-methyl' were not altered but the psychogalvanic response to thermal stimulation was reduced. The intensities of abstinence from dicodide or '6-methyl' were milder than would have been expected after withdrawal of morphine. These 2 drugs may therefore, have some advantages over morphine. Abstinence from morphinan was approximately equal to abstinence from morphine.



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7. The Relation of Electrolyte and Water Transfer Across the Arachnoid Membrane to Spreading Cortical Depression of Leao. — C. F. ESSIG and WADE H. MARSHALL, National Institute of Health, Bethesda, Md.

An attempt has been made to determine the effect on spreading cortical depression of removal of electrolytes from the subarachnoid space.

A solution of 9.95 per cent sucrose in distilled water is isotonic with respect to a solution containing 160 millimoles of NaCl per Kg. which has an osmotic pressure equal to human blood serum. Such a sucrose solution (9.95 per cent) was made to flow across the partially exposed arachnoid surface of one hemisphere for 20-30 min. before an electrical stimulation. Subsequent to this a static pool of phosphate buffered Ringer's solution was allowed to stand on the brain for another 15-30 min. The Ringer's solution was then washed off briefly and replaced by a new pool of 9.95 per cent sucrose. Then another electrical stimulation was performed within 1-2 minutes. Thus one stimulation followed what may be a dialyzing procedure and the other stimulation followed ion, and possibly water replacement by Ringer's solution.

The results obtained with such a technique definitely point to an accentuation of the spreading depression phenomenon following exposure to flowing sucrose. In approximately 64 per cent of the stimulations the contrast was absolute or completely positive. Thus, on immediate stimulation in static sucrose following exposure to Ringer's solution no spreading depression was obtained, but after flowing sucrose electrical stimulation produced spreading depression. In twenty-six per cent of cases, the contrast was not absolute because partial or occasional total reactions occur after Ringer's. In 10 per cent of the stimulations there was no obvious effect noted after exposure to flowing sucrose.

Other effects of this technique, such as accentuation of abnormal wave production and brain wave recovery, are being investigated.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 9, No. 1, March, 1950

Experimental addiction to barbiturates (motion picture). HARRIS ISBELL, SOL ALTSCHUL,* C. H. KORNETSKY,* H. F. FRASER,* H. G. FLANARY,* A. J. EISENMAN, A. WIKLER AND HARRIS HILL.*
Research Division, USPHS Hospital, Lexington, Ky.

Five former morphine-addict volunteers received barbiturates for 92-144 days. The highest daily dosages attained were 1.8, 1.8, and 3.8 gm. daily of seconal, pentobarbital, and amytal respectively. While chronically intoxicated, all patients showed impairment of mental ability, increased emotional lability, infantile behavior and confusion. No toxic psychoses were observed while patients were taking the drug. Neurological signs included nystagmus, dysarthria, ataxia in gait and station, and depression of superficial abdominal reflexes. The effects of the same dose of the drug varied widely from day to day and was partially dependent on food intake. Partial tolerance was observed. In the electroencephalogram the percentage of β waves was increased. Following withdrawal of barbiturates, neurological signs disappeared and weakness, anxiety, anorexia, nausea, vomiting, rapid weight loss, fever, elevation of NPN's, convulsions (4 of 5 patients) and a psychosis (4 of 5 patients) resembling alcoholic delirium tremens were observed. During withdrawal, the percentage of β waves was reduced in the electroencephalogram and paroxysmal bursts of slow waves appeared. Recovery was complete.

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ADDICTION POTENTIALITIES OF ISOMERS OF 6-DIMETHYLAMINO-4-4-DIPHENYL-3ACETOXY-HEPTANE (ACETYL METHADOL).

H. F. FRASER AND HARRIS ISBELL

Research Branch, U. S. Public Health Service Hospital, Lexington, Ky. (National Institute of Mental Health).

The drugs studied were the alpha forms of acetyl-l, -d and -dl-methadol. The l-antimer was synthesized from l-methadone, the d-antimer from d-methadone.

Thirty mg. of the dl form or 15 mg. of the l form subcutaneously, induced intense morphine-like euphoria, which began 30 minutes after the injection and persisted for 30 hours, in 10 former morphine addicts. Euphoria did not appear until nine hours after 30 mg. of the d-antimer were administered subcutaneously or intravenously. After oral administration of 30-40 mg. of the d form, euphoria appeared in 1-2 hours. After either method of administration, euphoria persisted 30-48 hours. Cumulative effects were observed after 15 mg. of the d-antimer twice daily for three days. All forms were effective in relieving and suppressing abstinence from morphine.

Twenty to 60 mg. of the d-antimer daily (given orally in two doses) prevented appearance of abstinence symptoms in 10 patients addicted to 160-400 mg. of morphine subcutaneously daily. These patients were stabilized for two weeks on the d-antimer and then the drug was abruptly and completely withdrawn. After two days, a mild withdrawal syndrome, similar to abstinence from methadone, appeared.

Reprinted from J. Pharmacol. & Exper. Therap.,
101: (1) 12 (Jan.) 1951.



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STUDIES ON ANXIETY PRODUCED BY ANTICIPATION OF PAIN.
I. EFFECTS OF MORPHINE. H. E. Hill, C. H. Kornetsky,
H. G. Flanary and A. Wikler. National Institute of
Mental Health of the National Institutes of Health,
Public Health Service. (Research Division, U. S. Public
Health Service Hospital, Lexington, Ky.)

In 22 post-addicts, hand reaction times to visual stimuli on days without morphine were compared with those after subcutaneous injection of 15 mg. of the drug under the following conditions: (a) the subjects were motivated only by a general knowledge of their performance, and (b) the subjects were penalized by self-administered brief, but strong electroshocks to one hand immediately after each response which was slower than the lowest previous median value. The fastest reaction times occurred in non-morphinized subjects who were not penalized for slow reaction times. Morphine alone slowed reaction times significantly. Electric shock penalties in non-morphinized subjects also slowed reaction times significantly. However, when electric shock penalties were delivered to morphinized subjects, reaction times were not slowed above that level effected by morphine alone during the first one and one-half hours after injection of the drug; indeed, in some subjects reaction

times under these conditions were faster than either after morphine alone or when the subjects were penalized with electric shocks when morphine was not administered. It is concluded that morphine reduces the disruptive effects on performances which are consequent to anxiety produced by anticipation of pain. This may represent an important aspect of the analgesic action of morphine.

J. Pharmacol. & Exper. Therap., 101: (1) 17 (Jan.) 1951.

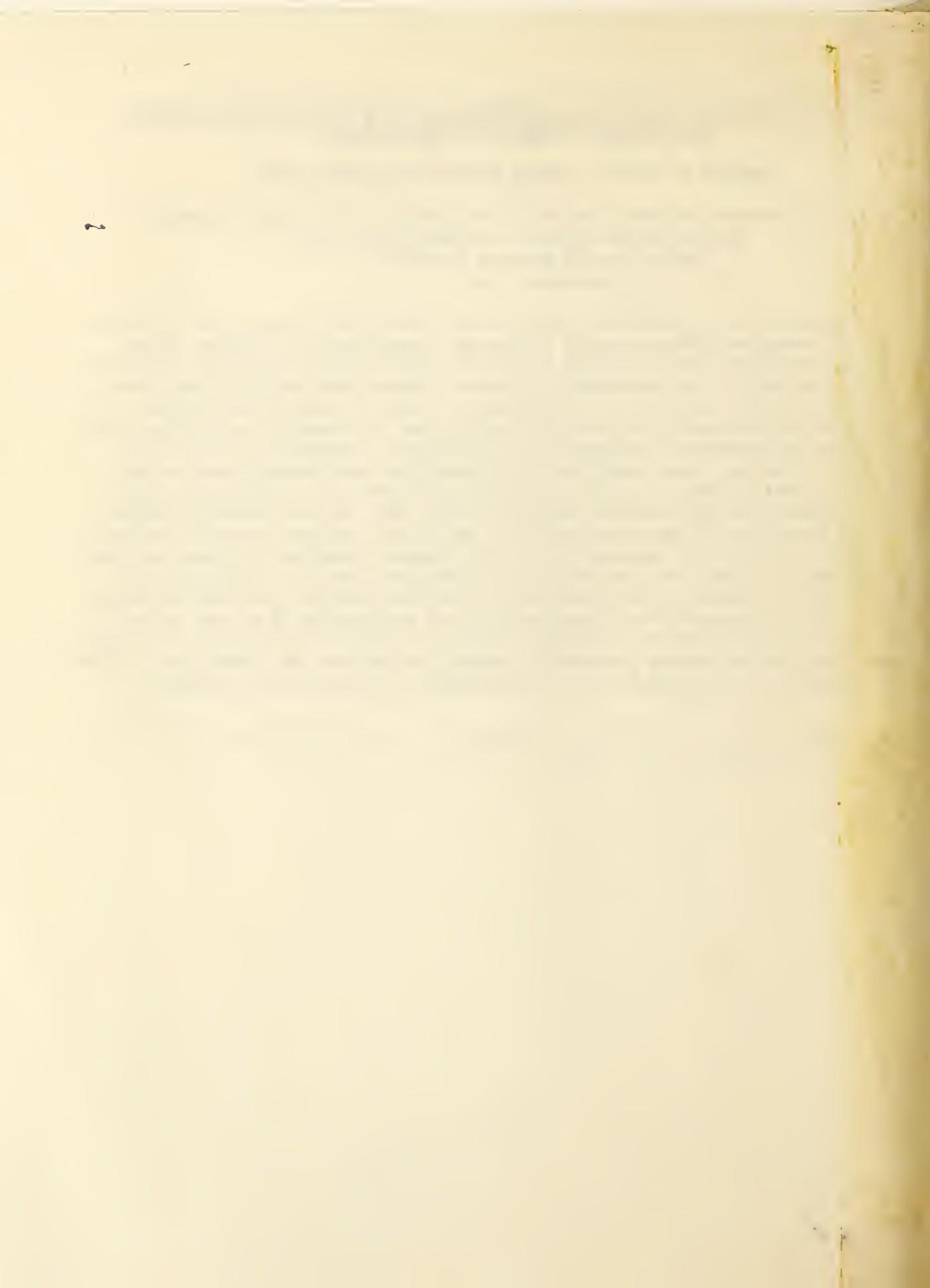
COMPARATIVE EFFECTS OF MORPHINE, MEPHENESIN AND THIOPENTAL ON SKIN-TWITCH
AND HINDLIMB REFLEXES IN SPINAL DOGS.

RAYMOND W. HOULE, ABRAHAM WIKLER AND SAMUEL IRWIN

National Institute of Mental Health of the National Institutes of Health,
Public Health Service, Research Branch, U.S.
Public Health Service Hospital,
Lexington, Ky.

Physiologic and anatomic studies demonstrate that in dogs, the cutaneous maximus response ("skin-twitch") to thermal irradiation or clamping of the skin is integrated over a spinal reflex arc whose sensory receptive field extends from D-2 to L-5 dermatomes and whose efferent arm emerges solely from C-8 ventral root. After spinal transection above C-8 segment the pattern of this reflex was essentially unaltered and it was depressed by effective doses of morphine, methadone, mephenesin, benzimidazole, pentobarbital and thiopental. However, these drugs could be classified into three groups on the basis of their effects on hindlimb reflex patterns: (a) morphine and methadone enhanced the ipsilateral extensor thrust, had few and variable effects on the knee jerk and depressed markedly the flexor, crossed extensor and Phillipson's reflex; (b) mephenesin and benzimidazole enhanced the knee jerk but depressed all other reflexes studied; (c) pentobarbital and thiopental progressively depressed all reflexes though the knee jerk was the last to disappear. It is concluded that depression of the skin-twitch by a drug is not necessarily an indicator of analgesic action. However, the effects of a given agent on hindlimb reflex patterns in chronic spinal dogs may enable one to predict whether it is likely to act like morphine, mephenesin or thiopental.

J. Pharmacol. & Exper. Therap., 101(1)18(Jan.) 1951.



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Alpha rhythms and sleep patterns in the electroencephalograms of patients after frontal lobotomy. ABRAHAM WIKLER, National Institute of Mental Health, the National Institutes of Health, Public Health Service (Research Division, U. S. Public Health Service Hospital, Lexington, Ky.)

In tracings from scalp leads anterior to the plane of frontal lobectomy performed through superior frontal burr holes, alpha activity was seen in a few records. After oral secanal 0.1 - 0.2 Gm., alternating 12-18 cps. "spindles" and slow activity was seen regularly. Intravenous pentothal 0.250 Gm. produced moderate voltage continuous fast (about 20 cps.) activity.

Reprinted from EEG Clin. Neurophysiol., 3: (1) 101, 1951.



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Reprinted from FEDERATION PROCEEDINGS
March, 1951, Vol. 10, No. 1, Part I
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Action of acetylcholine on cerebral cortex of cats and monkeys. CARL F. ESSIG (introduced by WADE H. MARSHALL). *Natl. Inst. of Mental Health, Natl. Insts. of Health, Bethesda, Md.* Acetylcholine chloride in strengths ranging from 2-20% produces a localized depression of normal electrocorticographic activity when applied to the cerebral cortex. The depression shows little or no effect on areas remote to the site of application and can be obtained from any region on the dorsal convexity of the cerebral hemisphere. The local diminution in brain wave activity does not show an associated significant change in the cortical d.c. potential. The local nature of the brain wave changes and the lack of a significant direct voltage variation serves to differentiate the acetylcholine effect from the spreading depression of Leão. The depressant action may be followed by local high frequency large amplitude spikes often resembling grand mal seizure patterns. The appearance of such local signs of stimulation is not constant. Topically applied 1% eserine sulfate appears to accentuate the depressant action of acetylcholine. Atropine abolishes the depressant action of acetylcholine more consistently than it counteracts the spiking activity. In addition, atropine sulfate abolishes the depression in systemic blood pressure which follows the topical application of acetylcholine to the cerebral cortex. The blood pressure diminution increases with the strength of the acetylcholine and the volume applied. The decrease in blood pressure occurs without regard to the cerebral region to which the acetylcholine is applied and is accentuated by previous eserization.



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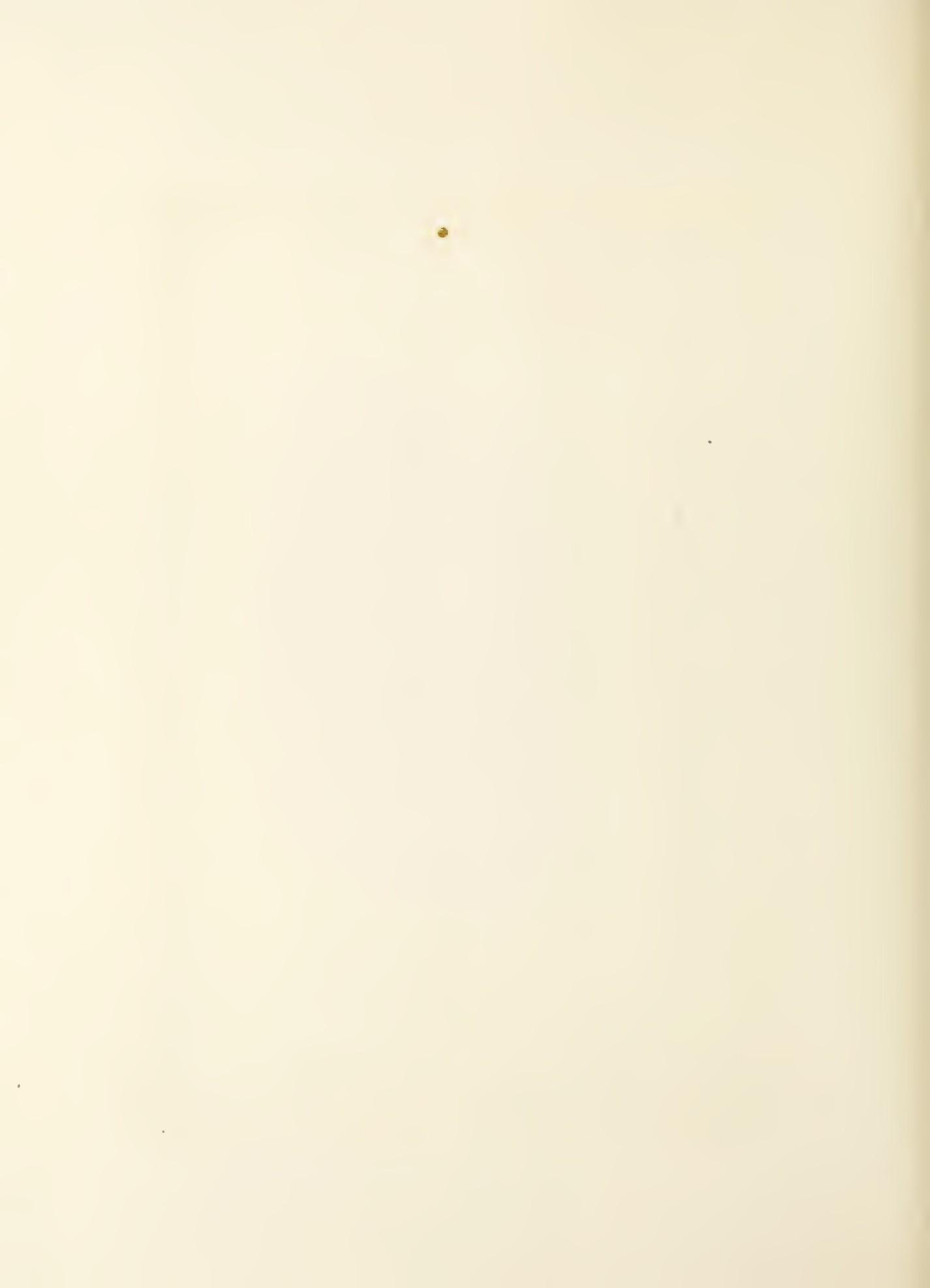
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Reprinted from FEDERATION PROCEEDINGS
March, 1951, Vol. 10, No. 1, Part 1
Printed in U. S. A.

Effect of addiction to morphine on excretion of water and electrolytes. ANNA J. EISENMAN.
Research Branch, US Public Health Service Hosp., Lexington, Ky.

Two subjects were placed on a low sodium diet. Three control days were followed by 20 days when they received 30 mg. of morphine 4 times daily. The subjects drank 1500 cc. of water and had an intravenous injection of 1000 cc. of glucose daily. On the first day of addiction there was a 60-90% decrease in the excretion of water, sodium and chloride. *Subject 1* showed decreased excretion for 4 days, reached control values on the 5th day, exceeded them on the 6th day. Thereafter, excretion of these substances was practically normal, with minor day to day variations. In *Subject 2*, water excretion was decreased for the first day only. For 6 days, there was very low sodium and chloride excretion. Thereafter, from the 8th to the 20th day, he showed a fluctuating excretion of salt, in general higher than during the control period. During sodium retention, potassium excretion exceeds its normal ratio of about 40% of the sodium excretion. In one subject it reached 500% at one time and did not regain the normal ratio until the 7th day. In the other subject, it had returned to its normal ratio in about 3 days. This is probably not an addiction effect, since the same phenomenon has been observed in other conditions of sodium and water retention. In general, it may be said that tolerance to the anti-diuretic effects (retention of water, sodium and chloride) of morphine is reached after about one week of addiction.





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Reprinted from FEDERATION P~~ROCEEDINGS~~
March, 1961, Vol. 10, No. 1, Part 1
Printed in U. S. A.

Cortisone therapy in barbiturate abstinence syndrome. H. F. FRASER,* H. ISBELL, A. WIXLER,
A. J. EISENMAN AND C. H. KORNETSET.* Research Branch, U. S. Public Health Service Hosp., Lexington, Ky.

Patient A was actively addicted to barbiturates and opiates. During his current hospital admission he was given only minimal amounts of pentobarbital during morphine withdrawal. A withdrawal-type grand mal convolution appeared on the 12th day. Secobarbital was then administered in increasing doses to a level of about 2.5 gm. daily, and maintained from the 21st through the 45th day. No significant symptoms of intoxication developed. A withdrawal psychosis consisting of confusion, visual and auditory hallucinations occurred on the 15th and 16th days, with a mild recurrence on the 25th day. On the 49th day, secobarbital was discontinued abruptly. Cortisone, 100 mg., was given intramuscularly 24 and again 5 hours prior to withdrawal. After 18 hours abstinence, anxiety, pass-pointing and tremors developed. Cortisone dosage was increased to 300 mg. daily and symptoms were relieved. Cortisone was continued for 2 weeks in a total dose of 2325 mg. He improved progressively and showed no signs of convulsions or psychosis and was discharged on the 66th day. Patient B was actively addicted to alcohol, opiates and barbiturates. His hospital course was analogous to A except that secobarbital was discontinued abruptly and no cortisone was administered. After 48 hours of abstinence, a grand mal convolution appeared. Cortisone therapy was then instituted and a total of 1400 mg. was given in 3 days. No further seizures appeared but psychosis developed on the 3d day of treatment and persisted for 3 days, following which progressive recovery occurred. Further clinical electroencephalographic, psychological and biochemical studies are in progress.

A PRELIMINARY STUDY OF THE EFFECTS OF ANXIETY AND MORPHINE ON DISCRIMINATION OF PAINFUL STIMULI. H. E. Hill, C. H. Kornetsky, H. G. Flanary and A. Wikler. National Institute of Mental Health, of the National Institutes of Health, Research Branch, USPHS Hospital, Lexington, Ky.

The effects of subcutaneous injection of 15 mg. of morphine on the ability of subjects (post-addicts) to estimate intensity of pain were studied under two conditions: (a) proceeding with the experiment without familiarizing the subjects with the potentially fear-inspiring experimental situation; (b) preceding experimentation with reassurance, demonstrations and explanations designed to allay apprehension and also permitting the subject to administer to stimuli to himself. Under all conditions, 15 electric shock stimuli of standard strength, followed one hour later by 6 successive series of stimuli of variable strength were delivered to one hand of each subject, who was required to state whether the shocks were stronger or weaker than the standard. Under condition (a) the subjects tended to overestimate the intensity of applied shocks, and this error was reduced by morphine. Under condition (b) overestimation of the intensity of applied

was less, and morphine had no significant effect thereon. Tentative conclusions are drawn that (1) anxiety sensitizes the organism to stimuli that have particular values; (2) morphine does not materially alter the differential perception threshold for electric shock stimuli when anxiety has been dissipated; (3) morphine reduces anxiety related to pain; (4) the possible influence of anxiety upon sensory thresholds should be taken into account in investigations of this type. The validity of these conclusions is being tested by further experimentation.

Fed. Proc., 10: (1) 309 (Mar.) 1951.

2091

Reprinted from FEDERATION PROCEEDINGS
March, 1951, Vol. 10, No. 1, Part 1
Printed in U. S. A.

Effects of large doses of N-allylnormorphine on man. ABRAHAM WIKLER. Research Branch, USPHS Hospital, Lexington, Ky.

In 12 post-addicts, subcutaneous injection of 30-75 mg. of N-allylnormorphine produced lethargy, mild drowsiness, vivid daydreams and dysphoria varying in intensity from vague anxiety to acute panic. The content of daydreams and degree of dysphoria varied in individuals and in the same subject on different days. All complained of inability to repress such daydreams, whose content appeared to be related to the degree of dysphoria. Miosis appeared in all subjects, pseudoptosis and sweating on forehead, palms and soles in most, while experiences of nausea, heaviness in the limbs, and hot and cold flashes were more variable. In 6 subjects the electroencephalogram remained essentially unchanged. In 2 others, in whom dysphoria was intense, alpha activity was sharply reduced. Intravenous injection of 30 mg. of morphine reduced only slightly the subjective changes produced by N-allylnormorphine. Intravenous injection of 0.1-0.2 gm. of sodium pentobarbital promptly and permanently abolished dysphoria and daydreaming but enhanced the drowsiness produced by N-allylnormorphine. Subcutaneous injection of 30 mg. of morphine 8 hours before, or 60 mg. of morphine 12 hours before, did not alter the effects of subsequent injection of 30-60 mg. of N-allylnormorphine. In 6 subjects, average changes during a 3-hour period after medication were as follows:

DRUG	TEMP. °C.	CARD. RATE PER MIN.	RESP. RATE PER MIN.	CIRC. EOSINO- PHILES
(a) Morph. mg.	30	-0.2	-2.7	-2.8 +36.9%
(b) N-allyl mg.	60	-0.5	-8.3	-1.7 -4.9%
(a) & later, (b)	1 hr.	-0.5	-3.3	-2.5 +16.5

Comparative effects of morphine on former morphine addicts and non-addicts.

H. F. Fraser* and Harris Isbell, Addiction Research Center,

U. S. Public Health Service Hospital, Lexington, Kentucky. (National
Institute of Mental Health).

The effects of 20 mg. of morphine sulfate, administered subcutaneously, on a group of 20 non-addicts were compared with those on a group of 24 former morphine addicts who had been abstinent from morphine for at least six months. Observations were made over a 24-hour period and included pupillary size (determined photographically), rectal temperature, pulse rate, respiratory rate, systolic blood pressure and the incidence of nausea and vomiting. There were no statistically significant differences between the responses of the two groups respecting any of these measures, except rectal temperature which was depressed to a greater extent in the non-addict group. The incidence of nausea and vomiting was higher in the non-addicts but the difference was not statistically significant.

The implications of these results will be discussed.

Presented interim meeting of American Society for Pharmacology and Experimental Therapeutics, Omaha, Nebraska. October 15, 16, 17, 1951.

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Human pharmacology and addiction liability of derivatives of 3-hydroxy-

N-methylmorphinan. Harris Isbell and H. F. Fraser,* Addiction

Research Center, Public Health Service Hospital, Lexington, Kentucky.

(National Institute of Mental Health)

Three to 4 mg. of l 3-hydroxy-N-methylmorphinan tartrate (Ro 1-5431)

and 20 mg. of dl 3-methoxy-N-methylmorphinan hydrobromide (Ro 1-5470) induced euphoria in non-tolerant former morphine addicts, which was roughly equivalent to the euphoria following administration of 30 mg. of morphine sulfate to the same subjects. Oral administration of Ro 1-5431 was less effective than subcutaneous or intravenous administration, whereas oral administration of Ro 1-5470 was at least equally as effective as subcutaneous or intravenous administration. Five to 60 mg. of d 3-hydroxy-N-methylmorphinan tartrate (Ro 1-6794) did not induce euphoria or any other morphine-like effect.

Data on the effects of all three compounds on pupillary size, rectal temperature, respiratory rate and pulse rate will be presented.

Five to 7 mg. of Ro 1-5431 subcutaneously, and 45 mg. of Ro 1-5470 subcutaneously or orally, relieved signs of abstinence from morphine. Following withdrawal of Ro 1-5470 after substitution for morphine, abstinence appeared, which was slower in onset, milder and more prolonged than abstinence from morphine. Sixty to 75 mg. of Ro 1-6794 had no effect on abstinence from morphine.

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Reprinted from THE AMERICAN JOURNAL OF PHYSIOLOGY

LIBRARY, No. 3, December, 1951

Printed in U.S.A.

NIMH ADDICTION RESEARCH CENTER

PHS, Lexington, Kentucky

Components of striate reactions. CARL F. ESSIG,* WADE H. MARSHALL AND LLOYD B. WITKIN.* Natl. Inst. of Mental Health, Natl. Insts. of Health, Bethesda, Md. Bishop and O'Leary (*J. Neurophysiol.* 1: 391, 1938), Marshall, Talbot and Ades (*J. Neurophysiol.* 6: 1, 1943) and Marshall (*J. Neurophysiol.* 12: 277, 1949) have concluded that the first significant potential recorded on striate cortex following a single maximal (cortical response maximal) shock to the optic nerve is a sign of radiation activity and that all subsequent (4 events) are cortical in origin. On basis of relative resistance to depression by application of Novocain, mechanical pressure and enhancement by strychnine, Chang and Kaada (*J. Neurophysiol.* 13: 305, 1950) question the conclusion of the above authors and propose that the 2nd and 3rd events (3rd and 4th deflections in Chang's nomenclature) are also radiation spikes. This laboratory has reexamined the question using spreading depression and isotonic KCl as quick acting, reversible depressing agents. The spreading depression type of test for room air conditions has been reported previously (MARSHALL, *EEG & Clin. Neurophysiol.* 2: 177, 1950). The more precise cooling method of reversibly creating conditions for spreading depression has been applied and shows profound effects on all specified events except the first. A similar result is seen following application of a pool of isotonic KCl 8 mm. in diameter. We have found no evidence to support the interpretations of Chang and Kaada. As previously pointed out, the 2nd event (3rd of Chang's) shows some peculiarities including greater resistance to depression but the difference is not qualitative.

page 782



Reprinted from THE AMERICAN JOURNAL OF PHYSIOLOGY
Vol. 167, No. 3, December, 1951
Printed in U.S.A.

Spreading depression. WADE H. MARSHALL, CARL F. ESSIG* AND LLOYD B. WITKIN*. Natl. Inst. of Mental Health, Natl. Insts. of Health, Bethesda, Md.

A pool of buffered Locke-Ringer's containing 10 X normal concentration of K ions placed for 20 minutes on exposed cortex produces a condition allowing spreading depression reactions to be elicited and the reactions cross the relatively deep sulci of cat and monkey. The condition can be reversed by a 20-30-minute application of a pool containing K free Ringer's solution. Previous work (*J. Neurophysiol.* 14: No. 4, 1951), has shown that within minutes after exposure to room air the spreading depression reaction can be demonstrated on the surface of a gyrus but will not cross the central sulcus until the exposure has been prolonged for hours. An obvious common factor of room air drying effect and excess K ion is the immediate development of a hyperemic appearance of the cortex. Application of an 8-mm. diameter pool of isotonic KCl on the striate cortex of the cat results in a quickly developing (60-75 seconds) depolarization of 10 to 15 mv. greater than the Nernst solution difference potential. This is accompanied by severe depression of spontaneous activity and of cortical response to afferent stimulation. Superimposed on this high magnitude depolarization, minor cycles of depolarization often occur at periods of several minutes accompanied by corresponding changes in the already severely attenuated cortical response to afferent stimulation. These cycles are presumably recurring spreading depression reactions confined to the cortical region under the KCl pool. This effect of isotonic KCl is reversible.

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Reprinted from FEDERATION PROCEEDINGS
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Printed in U.S.A.

Recording seizure occurrence in experimental epilepsy. CARL F. ESSIG AND GEORGE L. BARNARD (introduced by WADE H. MARSHALL). *Natl. Insts. of Health, Natl. Inst. of Mental Health, U. S. Public Health Service, Bethesda, Md.*

Chronic recurrent epileptic seizures occur following the application of alumina cream to the cerebral cortex of Rhesus monkeys as described by Kopeloff, Barrera and Kopeloff. A method has been devised to record the onset, frequency and temporal incidence of the convulsions. An activity cage with sheet metal walls and a floor supported from below by compression springs was constructed. The monkey's movements resulted in vertical undulations of the floor which were transmitted via an attached lever and connecting wire to an ink writing pen. The pen working against spring tension wrote on EEG paper moving 2.4 cm/min. which permitted continuous recording. Preliminary observations were made on 2 monkeys prepared with alumina cream 6 months previously. During the postoperative period these animals had never been seen to convulse spontaneously or in response to administered stress. It is indicated from the activity records obtained that both animals are subject to spontaneous nocturnal convulsions. One monkey was observed 18 days during which 3 nocturnal seizures occurred. There were no diurnal convulsions during this period. The other monkey had a single nocturnal attack during 6 days of observation. In both animals the ictal episodes appeared to begin during a period of complete inactivity. However, complete immobility of the cage floor prior to a seizure does not necessarily indicate that the animal was asleep when the attack began.

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R-Reprinted from FEDERATION PROCEEDINGS
Vol. 11, No. 1, March, 1952
Printed in U.S.A.

PHS, Lexington, Kentucky

Blood nonprotein-nitrogen constituents during barbiturate addiction and withdrawal. ANNA J. EISENMAN, JEWELL W. SLOAN* AND H. F. FRASER.* NIMH Addiction Research Center, USPHS Hosp., Lexington, Ky.

Fifteen human subjects were studied. During withdrawal of barbiturates there is usually a transient (1-23 mg. %) rise of blood total nonprotein-nitrogen which may occur anytime from the 3rd to the 8th day of withdrawal. Following convulsive seizures during withdrawal, the serum uric acid shows striking rises, correlated with eosinopenia, sometimes increasing by 10 mg. %. The maximum increase in serum uric acid is reached 2-5 hours after a convulsion. Unless the level is reinforced by a 2nd or 3rd convolution, it decreases sharply at first, then more gradually to below control (addiction) values. The increase in uric acid usually precedes that in NPN and is not sufficient to account for the increment in the total NPN. The relation between whole blood and serum NPN and urea seems to be consistent throughout addiction and withdrawal. Creatine and creatinine (serum) changes were not significant. Some of the NPN increase is due to urea, the remainder of the increase is not accounted for by the constituents we have studied. The elevated uric acid values after withdrawal convulsions could be due to convulsions alone, unassociated with barbiturate withdrawal. Four psychiatric patients receiving electroshock for the first time were used as controls. These subjects received a series of 3 shocks at 2- or 3-hour intervals. Uric acid rose about 6 mg. after the second shock. The increase was further reinforced by the third shock of the series. The rate of falling off was variable.

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Vol. 11, No. 1, March, 1952

Printed in U.S.A.

N-allylnormorphine in treatment of methadone poisoning in man: report of two cases. H. F. FRASER,* ABRAHAM WIKLER, A. J. EISENMAN AND HARRIS ISBELL. NIMH Addiction Research Center, USPHS Hosp., Lexington, Ky.

Case 1. A Negro male aged 33, a former heroin addict, volunteered for an experiment in which he received 20 mg. methadone intravenously at 8:30 A.M. and again at 1:30 P.M. The latter injection induced nausea and weakness followed by sedation which progressed to deep sleep at 4:30 P.M. At 6 P.M. patient was comatose and respiratory rate was 3/minute. Neither artificial respiration nor 375 mg. nikethamide intramuscularly benefited the patient. At 7 P.M. deep tendon, gag and corneal reflexes could not be elicited and respiratory rate was 2/minute. Rectal temperature was 35.8°C, pulse was of good quality and the rate was 75/minute. Patient was given 40 mg. N-allylnormorphine intravenously. Four minutes later respiratory rate rose to 10/minute and 23 minutes after injection, rate was 23/minute. Seventy minutes after administration of N-allylnormorphine patient was very drowsy but could be aroused by vigorous stimulation. Shortly afterward he walked with assistance. Recovery was progressive and uneventful. Concurrently, another healthy Negro male received from the same bottle 20 mg. methadone intravenously at 8:30 A.M. and again at 1:30 P.M. He showed no unusual response. Case 2 is analogous to case 1 and will be described. These two cases illustrate the cumulative effects of successive, relatively large doses of methadone and the reversal of the resulting respiratory depression and coma by N-allylnormorphine. Since this amount of methadone has been given to more than 125 other post-addicts without significant poisoning, a considerable variation of susceptibility occurs.

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Vol. 11, No. 1, March, 1952
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af. 402

Effects of morphine and N-allylnormorphine on reflexes in dog and cat. ABRAHAM WIKLER AND R. L. CARTER.* NIMH Addiction Research Center, USPHS Hosp., Lexington, Ky.

In 18 chronic spinal dogs, morphine (2-100 mg/kg.) depressed flexor and crossed extensor reflexes markedly; the effects of N-allylnormorphine (0.2-100 mg/kg.) were similar but much less intense. Knee jerks were affected variably and slightly by both drugs. Extensor thrusts were unaffected by either drug, enhanced by morphine, or depressed by N-allylnormorphine. N-allylnormorphine antagonized the depressant effects of morphine on the flexor and crossed extensor reflexes. If N-allylnormorphine was given first, the subsequent depressant actions of morphine were usually blocked (interval between subcutaneous injections 45 ± 15 minutes). When 30 mg/kg. of N-allylnormorphine was injected subcutaneously 1 hour after 100 mg/kg. of morphine, a typical 'morphine abstinence syndrome' appeared both in the segments rostral to the level of transection, and in the paralyzed hindlimbs (5 experiments). Such abstinence syndromes were also observed within 20 minutes after subcutaneous injection of single doses of N-allylnormorphine in 3 'addicted' preparations. Two mg/kg. of the drug produced these effects after morphine had been administered regularly in doses of 2 mg/kg. q6h for 4 days. As addiction continued at the same morphine dose level, the abstinence syndromes which were precipitated by the same single dose of N-allylnormorphine increased markedly. In intact cats, 5 mg/kg. of N-allylnormorphine produced no notable changes in behavior but antagonized the 'motor excitant' effects of 5 mg/kg. of morphine. In acute spinal cats, N-allylnormorphine, 0.5-15 mg/kg., enhanced the flexor and crossed extensor reflexes, blocked depressant effects of morphine thereon, or reversed them if morphine was injected first.

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PP. 402 Hold
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Precipitation of 'abstinence syndromes' by single doses of N-allylnormorphine in addicts (motion picture). ABRAHAM WIKLER, R. L. CARTER,* H. F. FRASER* AND HARRIS ISBELL. NIMH Addiction Research Center, USPHS Hosp., Lexington, Ky.

During active addiction to morphine or methadone, acute 'abstinence syndromes' appeared after subcutaneous injection of single doses of N-allylnormorphine. In both morphine and methadone addicts, the syndrome resembled strikingly that which is observed after abrupt withdrawal of morphine, except that after N-allylnormorphine, withdrawal signs appeared within 15 minutes, reached peak intensity by 45 minutes and then subsided slowly. One hour after N-allylnormorphine, even intravenous injection of morphine or methadone had little ameliorating effect on the 'abstinence syndrome'. Such abstinence syndromes could be demonstrated by subcutaneous injection of single doses of 15 mg. of N-allylnormorphine as early as one week after experimental addiction to morphine 15 mg. or methadone 10 mg. four times daily. After stabilization on morphine (360 mg. per day) or methadone (140 mg. per day), severe abstinence syndromes were precipitated by 5 mg. of N-allylnormorphine. The most intense abstinence syndrome ever observed in this institution occurred when 30 mg. of N-allylnormorphine were administered subcutaneously to a subject who had been stabilized on 300 mg. of morphine per day. In contrast, definite withdrawal signs were precipitated by 15 mg. of N-allylnormorphine in meperidine addicts only when the total daily dose of meperidine was about 3000 mg. Further studies on the effects of N-allylnormorphine in the course of addiction to other narcotics are in progress.

FATAL TERMINATION OF BARBITURATES ABSTINENCE SYNDROME
IN MAN. H. F. Fraser, M. R. Shaver, E. S. Maxwell,
H. Isbell and A. Wikler. National Institute of Mental
Health Addiction Research Center, Public Health Service
Hospital, Lexington, Kentucky.

Seavers and Tatum (1931) and Fraser and Isbell
(unpublished) have observed that dogs chronically
intoxicated with barbiturates may die if barbiturates
are suddenly withdrawn. However, except for one case
reported in the German literature, no human deaths
which could be definitely attributed to barbiturate
withdrawal have so far been reported. The case herein
presented is that of a 49 year old male who had been
taking 5.0 grams of secobarbital daily for 4 months
prior to hospitalization. On admission he denied the
use of barbiturates and so was given only 0.1 to 0.2
grams pentobarbital daily during the first 5 days in the
hospital. He developed a severe barbiturate abstinence
syndrome characterized by vomiting, nervousness, tremor,
and visual and auditory hallucinations. On the 6th
hospital day his pulse was weak and thready with a
rate of 120-146 per minute. He was cyanotic with cold
hands and feet, and had continuous clonic movements of
all extremities. His blood pressure had dropped from
170/90 to 90/70 and body temperature in the axilla
was 107°F. Sodium amytal, 0.5 grams, was given intra-

venously three times and temporary relief was obtained twice. He expired on the 6th day. Gross pathology showed left cardiac hypertrophy and an enlarged liver, but gross observations of the tissues were inadequate to explain the cause of death. The principle histological findings were: cerebral encephalopathy with diffuse neural degeneration; cerebral edema; and marked fatty metamorphosis of the liver.

EFFECTS AND ADDICTION LIABILITIES OF THE ISOMERS OF
THE 3-METHYL ETHER OF DROMORAN. H. Isbell and H. F.
Fraser. National Institute of Mental Health Addiction
Research Center, Public Health Service Hospital, Lexington,
Ky.

As previously reported, the racemate of the 3-methyl ether of Dromoran produces strong morphine-like effects in nontolerant former morphine addicts, and relieves or suppresses signs of abstinence from morphine in addicted persons. One pair of optical isomers of this compound has become available for study. The levo-rotatory 3-methyl ether of Dromoran in doses of 10-20 mgm. induces morphine-like behavior in former morphine addicts, constricts the pupils, and depresses respiratory rate and minute volumes. The effects of l-3-methyl ether of Dromoran, like those of the racemate, develop more rapidly following oral administration as compared with hypodermic administration. l-3-Methyl-Dromoran is at least as effective as morphine in relieving signs of abstinence from morphine. Dextro-rotatory 3-methyl-Dromoran in dose ranging up to 100 mgm. subcutaneously and orally produced no perceptible morphine-like effects and did not cause pupillary constriction or respiratory depression. d-3-Methyl-Dromoran had no effect on

abstinence from morphine. It is concluded that 1-3-methyl-Dromoran has high addiction liability, whereas α -1-methyl-Dromoran is devoid of addiction potentialities.

J. Pharmacol. & Exper. Therapeutics, 106: (4) 397
(December) 1952.

654. 17-Ketosteroid excretion in a cycle of morphine addiction and withdrawal. ANNA J. EISENMAN, H. ISBELL, H. F. FRASER AND JEWELL SLOAN. NIMH Addiction Research Center, Public Health Service Hosp., Lexington, Ky.

Four male subjects were studied: a) during a control period, b) during the administration of three ascending single doses of morphine, c) during morphine addiction (5-10 wk), and d) during withdrawal and recovery (4 wk). Urinary creatinine, uric acid and 17 ketosteroids were determined. Forty-eight hours after the administration of 45 mg of morphine, there was a striking fall in the excretion of 17 ketosteroids. The response to 60- or 75-mg doses was less, followed, on about the 3rd day by a rebound to values higher than those of the control period. During addiction the average decrease in 17-ketosteroid excretion was 55%. Throughout control and addiction periods uric acid/creatinine ratios showed variations within the normal range. Following withdrawal of morphine, eosinophil counts fell to nearly zero (12-24 hr), 17-ketosteroid excretion increased 80 to 500% above addiction values (24-72 hr) and, in 2 subjects, uric acid/creatinine ratios increased (24-72 hr). 17-ketosteroid excretion returned to control levels during the 3rd and 4th wk following withdrawal. The changes observed are compatible with adrenal activation following withdrawal of morphine.

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1061. Chronic barbiturate intoxication. H. F.
FRASER, H. ISBELL, A. WIELER AND F. PESCOR.
*NIMH Addiction Research Center, PHS Hosp.,
Lexington, Ky.*

Nineteen male volunteers received 0.8 to 3.8 gm of secobarbital, pentobarbital or Amytal daily for 6 weeks or more. Dosage in each case was the maximum compatible with safe, ambulatory management. Following abrupt withdrawal, all 19 patients exhibited weakness, tremors, insomnia and electroencephalographic abnormalities; 15 had convulsions (1-4); 12 became delirious; 3 escaped both convulsions and delirium; 1 had a delirium but no seizure; and 4 had seizures but no delirium. Seventeen patients recovered without treatment within 10-14 days; 2 patients became so exhausted during a protracted delirium that re-intoxication with barbiturates followed by gradual reduction was necessary. In an effort to determine the minimal dosage of barbiturates required to produce physical dependence, 4 patients received 0.8 gm, 8 received 0.6 gm and one 0.4 gm of secobarbital daily for 42-120 days. Only mild intoxication was observed in patients receiving 0.6 to 0.8 gm daily. Following withdrawal, one patient in the 0.8-gm group had a seizure. The remaining patients had no seizures; delirium did not develop in any of these subjects and other symptoms were mild. Following withdrawal of secobarbital from 2 subjects who had received 0.2 gm nightly for a year, no significant symptoms were observed, indicating that chronic consumption of barbiturates in the customary therapeutic amounts does not produce significant physical dependence.

1097. Addiction liability of dithienylbutylamines. H. ISBELL, H. F. FRASER, AND A. WIKLER. NIMH Addiction Research Center, PHS Hosp., Lexington, Ky.

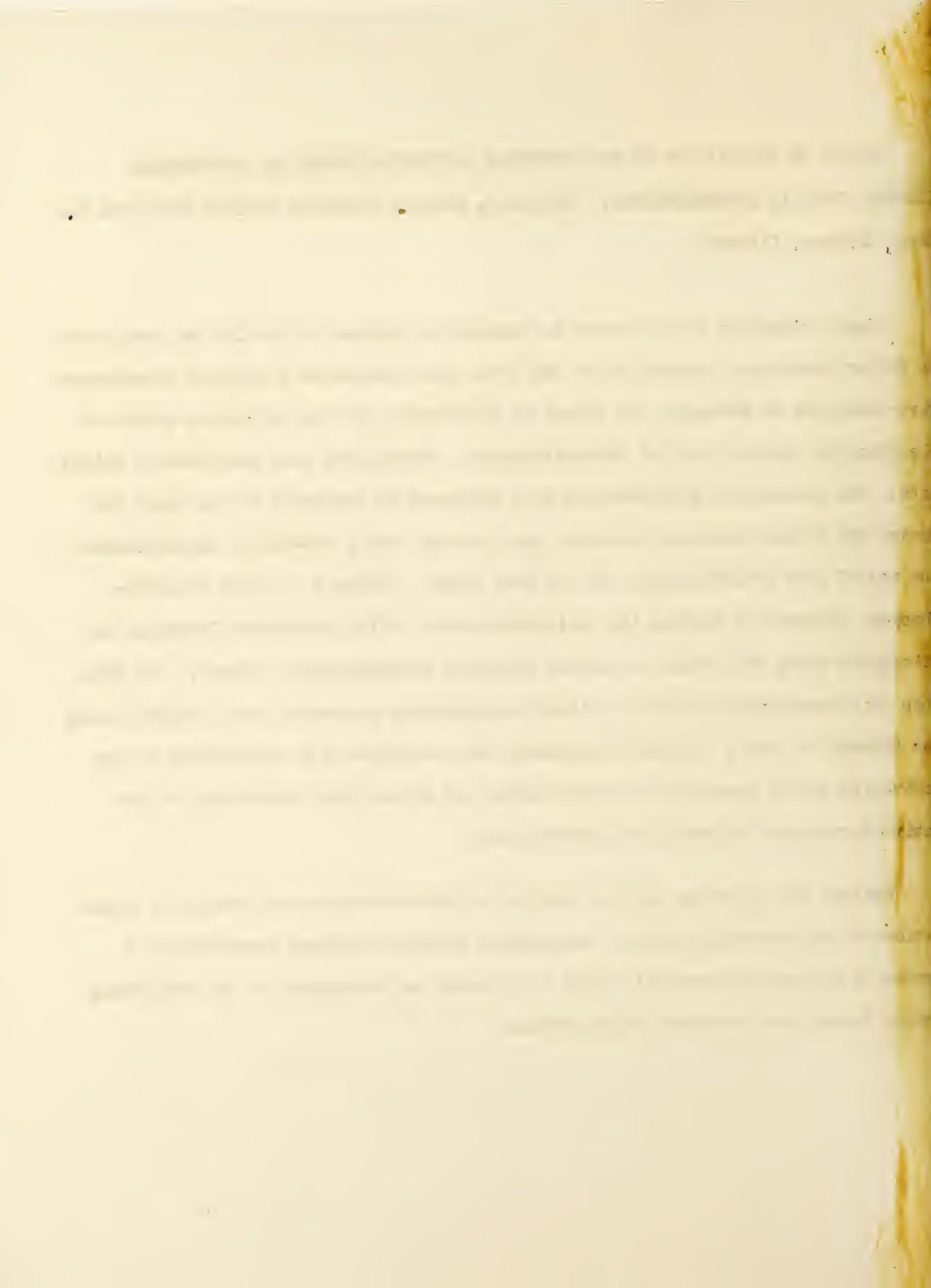
3-Ethylmethylamino 1:1-di-2'-thienyl-but-1-ene (No. 5145) and 3-diethylamino-1:1-di-2'-thienyl-but-1-ene (C-49) induced behavioral changes and symptoms in former morphine addicts resembling those seen after administration of morphine. 5145 was more potent in this respect than C-49. C-49 had little effect in alleviating abstinence from morphine whereas 5145 was quite effective. When substituted for morphine, C-49 suppressed abstinence from morphine partially but not completely. 5145 completely prevented the appearance of signs of abstinence when substituted for morphine. N-Allylnormorphine induced violent abstinence when administered to patients who were receiving 5145. Following withdrawal of 5145 substitution for morphine, a morphine-like abstinence syndrome became evident in 4-5 hr, reached maximum intensity in 12-14 hr and subsided in 5 days. The addiction liability of C-49 approximates that of codeine, whereas that of 5145 is about equal to that of morphine.



EFFECT OF STIMULATION OF THE RETICULAR ACTIVATING SYSTEM ON ELECTRICALLY INDUCED CORTICAL AFTERDISCHARGE. William R. Martin, Vernon G. Vernier and Klaus R. Unna, Chicago, Illinois

Since activation of the cortex as measured by changes in the EEG has been shown to follow electrical stimulation of the brain stem reticular formation, experiments were conducted to determine the effect of stimulation of this activating center on electrically induced cortical afterdischarges. Experiments were conducted in spinal cats. Ten consecutive electroshocks were delivered to the motor cortex using 100 cycles per second condenser discharge type current with a one-minute period between the end of each afterdischarge and the next shock. During 5 of these afterdischarges, selected at random, the activating center of the recticular formation was stimulated using 300 cycles per second condenser discharge type current. The duration of afterdischarges with and without accompanying activation were compared using the Student "t" test. Similar experiments were conducted with stimulation of the activating center preceding the electroshock and others with stimulation of the activating center following the electroshock.

Neither the character nor the duration of afterdischarge was changed by stimulation of the activating center. An atypical cortical response consisting of a series of spike-like potentials could be obtained on stimulation of the activating center during the post-ictal quiet period.



Use of measurements of miotic effects in evaluating analgesic drugs in man. H. F. Fraser, Harris Isbell, G. D. Vanhorn,* and T. L. Nash.* National Institute of Mental Health, Addiction Research Center, PHS Hospital, Lexington, Kentucky.

Measurement of the miotic effects is useful in determining the intensity and duration of action of a series of opiates and synthetic analgesics. The technique is as follows: Patients remained at bed rest in a completely darkened room for 15 minutes. The pupils and a centimeter ruler are then concurrently photographed, using a stroboscopic light with a flash duration of 1/5000 of a second. The pupillary diameter after 15 minutes in the dark is considered as 100 per cent for each subject and the amount of miosis due to an analgesic is calculated as the per cent of the control observation. Usually 10 men are employed in testing a placebo or analgesic. The method has been effective in comparing pharmacological effects by oral and subcutaneous routes. It permits a statistical comparison of several drugs and is most reliable when a series of drugs are tested in the same individual. While it is not specific, it is not affected by "residual tolerance" and results correlate well with the physical dependence supporting properties of analgesics. Correlations of miotic effect with clinical analgesia are inconsistent. It is most useful in evaluating analgesic drugs when employed in conjunction with other procedures, such as respiratory minute volume, and clinical observations for type and extent of euphoria induced.

Influence of dilantin and phenobarbital on the response of the cortex to stimulation of the activating center. William R. Marvin¹, Vernon D. Vermier² and Klaus R. Wina.
Dept. of Pharmacology, University of Illinois College of Medicine, Chicago 12, Illinois.

The elaboration of the bulbo-reticular activating system by Magoun and his associates has provided an anatomic entity that could be an important site of action of many drugs. It was our purpose to find what effects drugs, particularly anticonvulsants, may have on this system. This paper is a preliminary report on the effect of Dilantin and phenobarbital on the activating center. In this study electroencephalograms were taken on three types of preparations: (1) cats with an intact cortex and brain stem; (2) cats with their brain stem sectioned at the intercollicular level; (3) cats with a stereotactically oriented stimulating electrode in the activating center. Both Dilantin and phenobarbital were administered intravenously to cats in 10 mgm./kgm. doses at one-half hour intervals. Dilantin did not prevent activation of the cortex either in the normal EEG or in the preparation in which the activating center was stimulated electrically with doses up to 30 mgm./kgm. In equipotent doses Dilantin had little effect on the spontaneous cortical potentials of the "cerveau isole" preparation. Phenobarbital, on the other hand, produced 8-12 cycles per second sleep spindles in the normal EEG and in larger doses slowed the frequency of the component waves and decreased the frequency of recurrence of the spindles. A similar phenomenon was observed in the "cerveau isole" preparation but was accomplished with one-third the amount of phenobarbital. Phenobarbital markedly decreased the cortex's ability to respond to stimulation of the activating center and completely abolishes the response in doses that range from 40-70 mgm./kgm.

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677. Effects of ACTH and gonadotropin during a cycle of morphine addiction. ANNA J. EISENMAN, H. F. FRASER AND H. ISBELL. NIMH Addiction Research Center, PHS Hosp., Lexington, Ky.

Three human male subjects were studied before, during and after morphine addiction. Ten IU of ACTH were administered by 8-hr. infusion in 1 l saline; 1000 IU of chorionic gonadotropin were administered intramuscularly once daily for 5 days. The analyses included urinary 17-ketosteroid, creatinine and uric acid and blood eosinophil counts. Milligram increments of 17-ketosteroids following ACTH during addiction were slightly less in 2 subjects and markedly less in 1 subject than during pre- and post-addiction. Percentage rises during addiction were greater in 2 subjects and smaller in 1 subject. Increments in uric acid excretion were only slightly less during addiction than in periods of non-medication. Drop in the eosinophil count to 5% or less of the control value accompanied each administration of ACTH; the fall was slower during addiction. Reduction of the dose of ACTH to 5 or $2\frac{1}{2}$ units did not significantly alter the results. Chorionic gonadotropin caused a rise in 17-ketosteroïd excretion during, or from 1-3 days after, the course of injection. Both the milligram increment and the percentage rise were greater during addiction than during the control periods, with a slight tendency towards retardation of the effects during addiction. Lowered excretion of 17-ketosteroid during addiction (previously reported) suggests suppression of adrenal and testicular function. Results of the experiments show that the adrenal and testis are capable of response to specific hormonal stimulation during maintained morphine addiction.

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1126. Electrophoresis blood serum protein patterns of narcotic addicts and controls.

ROBERT L. CARTER, H. F. FRASER AND ANNA J. EISENMAN. *Natl. Inst. of Mental Health Addiction Research Center, PHS Hosp., Lexington, Ky.*

The electrophoretic patterns of fasting blood serum of 20 male narcotic addicts and 19 male non-addicts were determined using barbiturate 0.1 M buffer at pH 8.6. Serum was diluted 1 to 7 with buffer and dialyzed for 48 hr. at 10° C. A 6-ml cell was employed in a Tiselius apparatus (Model 3S, Perkin Elmer Corp.) using 3 watts. Photographs of ascending and descending limbs were made at 0, 60, 90, and 105 and 120 min. Photographs of the ascending limb after 105 min. were enlarged and the relative protein composition measured with a planimeter. Some patients were actively addicted when the sample was taken but all were in good general health. Histories of addiction ranged from 6-33 years' duration. Significant chronic infection and liver disease were excluded in all addicts and controls by clinical observation and by WBC count, sedimentation rate, ecephalin flocculation, thymol turbidity and icteric index determinations. The ratios of albumin and gamma globulin to total protein were 0.498 and 0.209 respectively for addicts, and for controls, 0.536 and 0.151. The relative reduction in albumin in addicts was statistically significant ($P < 0.05$) as was the relative increase in gamma globulin ($P < 0.0002$). However, these differences are not specific since there was definite overlapping between groups. Whether these differences in serum albumin and gamma globulin concentrations in addicts are due to opiate addition per se has not been determined.

2934

1127. Use of N-allylnormorphine in early demonstration of physical dependence on potent analgesics in dogs. R. L. CARTER AND A. WIKLER. *Natl. Inst. of Mental Health Addiction Research Center, PHS Hosp., Lexington, Ky.*

In experiments conducted in a grassy yard outdoors, or in a room provided with a sand-box, single doses of N-allylnormorphine 15 mg/kg produced little change in behavior of intact dogs, other than mild sedation. However, during addiction to morphine 5-10 mg/kg q6h or methadone 2-5 mg/kg q6h for periods of 7-90 days, marked changes appeared within 5-20 min. after subcutaneous injection of N-allylnormorphine 15 mg/kg or less. In its most complete form, this consisted of restlessness, lacrimation, rhinorrhea, yawning, salivation, vomiting, urination and marked tremors. Also, persistent digging, gnawing and rooting in the earth or sand occurred, after which the dogs rested briefly in the holes excavated before resuming the performance again, over a period of about 4 hr. However, considerable individual variation, qualitative and quantitative, was observed. 'Digging' behavior occurred in about 60% of experiments. In general, the changes became more severe as addiction proceeded, and in some cases, N-allylnormorphine produced incessant vomiting and marked prostration. The 'natural' abstinence syndrome which ensued 2-4 days after abrupt withdrawal of morphine or methadone following addiction periods of 42-88 days included listlessness, lacrimation, rhinorrhea, yawning, tremors, vomiting and sporadic 'digging'. By use of N-allylnormorphine and a large number of dogs, a useful rapid screening method for testing addiction liability of analgesics with opiate-like actions may be developed. However, the method was not effective in demonstrating acute 'abstinence' syndromes during addiction to meperidine 10 mg/kg q3h. Further studies are in progress.

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1169. Chronic intoxication of dogs with sodium barbital (motion picture). H. F. FRASER AND H. ISBELL. *Natl. Inst. of Mental Health Addiction Research Center, PHS Hosp., Lexington, Ky.*

Sixteen male and female dogs received orally once daily 106-168 mg/kg sodium barbital for 216-337 days. All dogs were started at lower doses but rapidly increased within 2-3 wk. to the maximum dose which each animal could safely maintain. One dog died during the intoxication phase; others were healthy throughout, except for intoxication. Following abrupt withdrawal, 14 animals had 2-29 grand mal convulsions and the group had 159 convulsions. The first convolution occurred from 2-5 days after stopping sodium barbital. Eleven dogs showed varying degrees of very abnormal and bizarre behavior (apprehension, fear, lack of recognition of attendants, and behaving as if reacting to nonexistent animals by growling, snarling, biting, and sexual acts without any appropriate stimulus to evoke any of these responses). One dog died from pneumonia in early abstinence, 1 died after the 29th convolution, all others recovered rapidly in about 2 wk., except that several showed excessive sexual interest for several months. The findings were confirmed in another experiment using 13 dogs. This study confirms the work of Seavers and Tatum in dogs and shows that the entire picture of barbiturate withdrawal in humans may be reproduced in experimental animals.

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p. 369

1216. Addictive properties of methadone derivatives. H. ISBELL AND H. F. FRASER. *Natl. Inst. of Mental Health, Addiction Research Center, PHS Hosp., Lexington, Ky.*

In non-tolerant former morphine addicts, alpha-l-methadol (derived from d-methadone) (I), and beta-d-acetyl-methadol (derived from l-methadone) (II), in doses of 50 to 60 mg orally or subcutaneously induced 'euphoria' and pupillary constriction. Effects of both drugs appeared slowly (4-9 hr.) but persisted for 60-72 hr. It was more effective orally than subcutaneously, whereas II was equally effective by both routes. Both drugs completely suppressed abstinence symptoms when substituted for morphine in strongly addicted patients; 1 daily oral dose of $\frac{1}{3}$ - $\frac{1}{2}$ the total daily morphine dosage sufficed for this purpose. Following abrupt withdrawal, mild abstinence appeared and subsided quite slowly. I and II possess high addiction liability similar to that of alpha-l-acetylmethadol. Doses of dl, l and d 2,2-diphenyl-4-dimethylamino ethyl valerate HCl (III, IV, V) and ethyl 2,2-diphenyl-4-dimethylamino butyrate HCl (VI) ranging up to 73 mg subcutaneously or orally did not induce definite morphine-like euphoria and did not relieve abstinence from morphine. III and V caused slight but definite pupillary constriction, whereas IV and VI did not. Addiction liabilities of these drugs do not exceed that of codeine.



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1217. Experimental chronic alcoholic intoxication (motion picture). H. ISBELL, H. F. FRASER, A. WIKLER, ANNA J. EISENMAN, R. E. BELLEVILLE AND T. L. NASH. *Natl. Inst. of Mental Health, Addiction Research Center, PHS Hosp., Lexington, Ky.*

Ten former morphine addict volunteers, who had no history of convulsions or psychotic episodes, drank 290-620 ml 95% ethanol diluted with water and fruit juice daily. Total daily alcohol intake was divided into 12-24 drinks. Patients were given high-quality, high protein diet supplemented with vitamin capsules. Prior to and during withdrawal, massive vitamin supplementation was given parenterally. Early in chronic intoxication patients were noisy, silly and emotionally labile; after 6 wk., they were much quieter and drinking to prevent tremors, which appeared if they had not had alcohol for several hours. Four patients who withdrew from the experiment after 7-35 days intoxication, did not have convulsions and/or delirium. Alcohol was abruptly withdrawn from the remaining 6 subjects after 45-87 days intoxication. Two of these had convulsions; 3 became frankly delirious; 2 had hallucinations but maintained orientation and insight; 1 escaped both convulsions and delirium. All 6 patients had weakness, tremors, etc., on withdrawal. These appeared before blood alcohol levels were zero. In 3 patients, blood alcohol levels were zero when they were consuming 13-16 ml of 95% ethanol hourly. When consuming 20-21 ml hourly, blood levels rose to 150-300 mg%. If this intake was maintained, blood levels gradually fell, after increasing to 22-23 ml/hr levels, rose again and, thereafter, did not fall. The experiments indicate that withdrawal of alcohol from chronically intoxicated persons will precipitate delirium tremens.

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1367. Effects of morphine on electric shock-conditioned inhibition of acquired feeding behavior in rats. A. WIKLER, H. E. HILL AND R. E. BELLEVILLE. *Natl. Inst. of Mental Health Addiction Research Center, PHS Hosp., Lexington, Ky.*

The methodological principle involved is based on previous demonstration that in man, morphine reduces behavior-disrupting anticipatory responses to painful stimuli. Rats, maintained at about 70% of satiation weight, were trained to obtain food, delivered aperiodically at about 2-min. intervals, by pressing a bar in a modified Skinner Box. Such bar-pressings were recorded cumulatively on a constant speed, slowly moving kymograph for 20-min. periods in each experiment. Later, a previously neutral tone, introduced about 10 min. after regular bar-pressing had begun, acquired the function of inhibiting this activity only for the period of its duration (4 min.) after repeated experiments in which it was followed by a strong electric shock delivered to the rat through the grid floor. By this procedure, bar-pressing during the tone period was reduced to a mean of 11% of the pre-tone rate. Subcutaneous injection of morphine, 4-10 mg/kg, restored such inhibited bar-pressing to 22-80% of the rate exhibited by the morphinized rat prior to introduction of the tone in each experiment. The effect varied directly with the dose, in spite of some decrease in the pre-tone rate of bar-pressing. With higher doses, activity was more impaired and erratic, although bar-pressing was restored to a median rate of 80%. The potential usefulness of this technic for analgesic testing purposes is currently under investigation.

Dgt. #3063

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Reprinted from SCIENCE, July 23, 1954, Vol. 120, No. 3108, page 153.

Anxiety Reduction as a Measure of the Analgesic Effectiveness of Drugs

A method that shows considerable promise for testing the analgesic potency of drugs has been developed recently at this laboratory. Previous techniques involving animals have been dependent upon measuring drug produced changes in reflexes or unconditioned responses. In contrast with these techniques, the present method provides a testing situation more analogous to that found in the clinic, because it is based upon a psychological principle that has been validated on man.

Previous studies of this series were designed to test the hypothesis that one necessary action of a potent analgesic is the reduction of anxiety associated with anticipation of pain [H. E. Hill *et al.*, *Arch. Neurol. Psychiat.* 67, 612 (1952)]. These investigations on man demonstrated that therapeutic doses of morphine (15 mg) significantly reduce behavior-disrupting anticipatory responses to painful stimuli. However, these techniques are not practical for the routine testing of drugs, since they are severely penalizing and utilize relatively large numbers of human subjects. It appeared possible, however, to develop a similar method for use with the laboratory rat.

Albino rats, maintained at approximately 70 percent of satiation weight, were conditioned to press a bar at a rapid rate in a modified Skinner Box. Food pellet reinforcements were available aperiodically at approximately 2-min intervals. Bar-pressings were recorded cumulatively on a slowly moving kymograph for the 20-min period of each test. After approximately 15 daily sessions, when the animals showed a high degree of conditioning, a 60-cy/sec tone was introduced 10 min after each test was begun. The tone was of 4 min duration and was terminated by a strong electric shock delivered to the rat through the grid

floor. This superimposed, classical conditioning procedure reduced bar-pressing during the tone to a mean of 11 percent of the pretone rates. Subcutaneous injections of morphine, 4 to 11 mg/kg, spaced at weekly intervals restored the inhibited bar-pressing to 22 to 80 percent of the response rate exhibited prior to the tone. The effect varied directly with the dose, despite some over-all decrease in frequency of response.

In general, then, after the animals were thoroughly conditioned, bar-pressing was disrupted or completely inhibited for the duration of the tone. This anticipatory effect of painful stimuli was reduced by morphine with the result that the animals continued to press the bar during the tone. The results are analogous to those of the earlier studies on human subjects and support the hypothesis that reduction of anxiety associated with anticipation of pain is one necessary action of a potent analgesic.

The usefulness of this technique for testing the analgesic properties of a wide range of drugs is currently under investigation. In contrast with other techniques in which animals are used, this method would appear to be more closely related to those employed in the clinic, since anxiety is an important component of clinical pain. Furthermore, several uncontrolled variables that are present in clinical investigations, such as suggestion and personal interaction, would be eliminated. In addition, the method might be used by pharmaceutical houses and in other settings in which clinical studies are not possible.

HARRIS E. HILL
RICHARD E. BELLEVILLE
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NIMH Addiction Research Center
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Lexington, Kentucky

18 January 1954.

CLINICAL AND ELECTROENCEPHALOGRAPHIC EFFECTS OF DRUGS
ON MAN AND DOG. A. Wikler, F. T. Pescor, National
Institute of Mental Health, Addiction Research Center,
PHS Hospital, Lexington, Ky.

The illustrations include sample EEG tracings and Clinical Notes made during studies on the effects of single doses of morphine, N-allylnormorphine, barbiturates, alcohol, mescaline and LSD-25 in man, the effects of chronic intoxication and withdrawal of meperidine and barbiturates in man, and the effects of single doses of pentobarbital, morphine, N-allylnormorphine, methadone, atropine and nikethamide in unanesthetized dogs. They are presented for the purpose of directing attention to the relatively stereotyped, non-specific electroencephalographic effects of a number of drugs which produce marked and widely differing changes in behavior. In general, such agents either have no significant effect on the EEG, or they produce diffuse, bilaterally symmetrical changes in the direction of increased synchronization or desynchronization. In contrast, they produce a variety of ideational, affective, sensorial, motor and autonomic changes, the pattern of which is highly predictable for a given drug. This suggests that the mechanisms regulating the EEG are only indirectly related to those subserving behavior, and that they

serve functions related to cerebral homeostasis -
(Wikler, A.: Clinical and Electroencephalographic
Studies on the Effects of Morphine, N-allvlnormorphine
and Mescaline in Man.)

Trans. Am. Neurol. Assn., Richmond, Va., pp. 170-173,
1954.

ADDICTIVE PROPERTIES OF MORPHINE DEPIVATIVES. H. F. Fraser
and H. Isbell, National Institute of Mental Health,
Addiction Research Center, PHS Hospital, Lexington, Ky.

No evidence of morphine-like effects were observed in 18 non-tolerant former morphine addicts after oral administration of 25 to 600 mgm. of the myristyl ester of benzylmorphine (I). Three of the patients developed an erythematous macular rash which faded in 24 hours. In doses of 100 mgm. every six hours, I failed to prevent the appearance of signs of abstinence from morphine in 4 patients who had been receiving 240 to 320 mgm. of morphine sulfate daily.

1.5 to 2.0 mgm. of dihydro-hydroxymorphinone ("Numorphan" II) induced intense morphine-like effects in 5 nontolerant former addicts. 6 mgm. of II subcutaneously every three hours completely suppressed abstinence in 2 patients who had been receiving 60 mgm. of morphine every six hours. Three nontolerant patients received II for 18 days, the dose being increased from 0.5 mgm. to 4.0 mgm. subcutaneously every three hours. N-allylnormorphine precipitated abstinence in both groups. Following withdrawal of II, severe abstinence was evident in six hours in all the patients.

It was concluded that I has low (or no) addiction liability, whereas II has high addiction liability.

ADDICTION LIABILITY OF 4-4-DIPHENYL-6-DIMETHYLAMINO-HEXANONE-3. H. Isbell and H. F. Fraser. National Institute of Mental Health Addiction Research Center, Lexington, Kentucky.

Definite evidence of morphine-like effects were observed after administration of doses of 45 to 60 mgm. of 4-4-diphenyl-6-dimethylamino-hexanone-3 (1), either orally or subcutaneously, to 23 nontolerant former morphine addicts. Single doses of 60 to 90 mgm. of 1 subcutaneously partially relieved symptoms of abstinence from morphine in 4 patients who had been receiving 240 to 480 mgm. of morphine sulfate daily. Administration of 60 mgm. of 1 subcutaneously every six hours effectively suppressed appearance of symptoms of abstinence in 2 patients who had been stabilized on 240 to 320 mgm. of morphine daily.

It was concluded that 1 has addiction liability which is less than that of methadone but greater than that of codeine.

FJH 165

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1049. Chronic meperidine intoxication in intact and chronic spinal dogs. R. L. CARTER AND A. WIKLER. Natl. Inst. of Mental Health Addiction Research Ctr. PHS Hosp., Lexington, Ky.

In 6 intact dogs, meperidine 10 mg/kg (subcutaneously) q 3 h produced mild sedation during the first few days, but little change in behavior after 57 days of addiction. N-allylnormorphine, 15 mg/kg did not precipitate abstinence phenomena, nor were such observed after abrupt withdrawal of the drug. In 3 intact dogs, meperidine, 15-20 mg/kg q 3 h produced occasional convulsions, and frequently, muscular twitches, exaggerated startle responses and extensor rigidity during chronic intoxication for as long as 126 days. In 2 of these, N-allylnormorphine, 15 mg/kg failed to precipitate abstinence phenomena, while equivocal changes were observed in the other. No clearcut abstinence changes appeared on abrupt withdrawal of the drug. In 4 chronic spinal dogs, single doses of meperidine (10 mg/kg) produced morphine-like changes in hindlimb reflexes: depression of flexor and crossed extensor reflexes, enhancement of extensor thrust, with little change in knee jerks. On meperidine, 10 mg/kg q 3 h, tolerance to the depressant effects developed by the 7th day. Unlike morphine, however, twitches and extensor spasms of the hindlimbs, either spontaneous or induced by tapping bony prominences caudal to the spinal cord transection, appeared by the 10th day and became increasingly severe during 43 days of continued meperidine intoxication. Also in contrast to morphine, N-allylnormorphine, 15 mg/kg did not precipitate abstinence changes during intoxication, and no hindlimb 'running' movements appeared on abrupt withdrawal of meperidine. The failure to demonstrate physical dependence on meperidine in dogs may be due to the limits which the toxic (convulsive) action of the drug places on dosage and frequency of administration.

1099. **Morphine antagonists.** H. F. FRASER AND H. ISBELL. *Natl. Inst. of Mental Health Addiction Research Ctr., PHS Hosp., Lexington, Ky.*
The subjective effects induced by N-allyl diacetylnormorphine (I), N-propyl-dihydronormorphine (II), D-3-hydroxy-n-allylmorphinan (III), L-3-hydroxy-n-allylmorphinan (IV), L-3-methyl ether of N-allyl-morphinan (V), L-3-acetoxy-n-allylmorphinan (VI), and L-3-hydroxy-n-propargyl-morphinan (VII) were studied, using nontolerant former morphine addicts as subjects. All drugs except III, which was inert, induced subjective sensations resembling those reported after 10 mg of Nalorphine subcutaneously. The effective doses were: 10 mg of I, 12.5-20 mg of II, 5.0 mg of IV, 2.5 mg of V, 3.0 mg of VI, and 4.0 mg of VII. The subjective effects induced by I and II were more morphine-like than those induced by Nalorphine. The subjective sensations induced by VII resemble to some extent those induced by Meperidine or Dilaudid. I and VII were relatively ineffective when given orally. II, IV, V and VI were effective orally in doses approximately twice the effective subcutaneous doses. All drugs except III precipitated mild to moderate abstinence in patients addicted to 240 mg of morphine daily, or more. The effective subcutaneous doses were: I, 5 mg; II, 7 mg; IV, 2 mg; V, 2 mg; VI, 1.5 mg; VII, 1.0 mg. I was relatively ineffective in precipitating abstinence when administered orally. II, IV, and V were effective when given orally in doses of 7 mg, 8 mg and 3-5 mg. VI and VII were not tested orally. IV and V are of interest because of prolonged effect (as compared with Nalorphine) and because they are orally effective. VII is of interest since it produces significant analgesia in mice (EDDY, 1954).

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1145. Tolerance to diethylamide of lysergic acid (LSD-25). H. ISBELL, H. F. FRASER, A WIKLER AND R. E. BELLEVILLE. *Natl. Inst. of Mental Health Addiction Research Ctr., PHS Hosp., Lexington, Ky.*

There is practically no information concerning chronic intoxication with the diethylamide of lysergic acid (LSD-25). It was noted that when former morphine addicts were given 1 or more doses the degree of LSD-effect declined rapidly. Eleven patients were given 10 μ g, increasing to 30 μ g of LSD orally twice daily for 3 days. On the 4th day, 75 μ g of LSD induced only mild mental effects. After 3 days of placebo administration, 75 μ g of LSD induced marked to severe mental effects. In another experiment, administration of 20 μ g of LSD, increasing to 75 μ g once daily, also induced a high degree of tolerance to the mental effects. In 12 patients, pupillary size, amplitude of knee jerk and systolic blood pressure were measured. Mental effects were gauged by means of a questionnaire. These patients received LSD once daily for 7-42 days. In 5 cases, the dose was increased from 50 to 180 μ g of LSD daily; in 6 cases, dose was maintained at 1-2 μ g/kg orally daily; 1 patient withdrew from the experiment after 9 days. In all patients, tolerance to all the effects measured was evident in less than 7 days. Once tolerance was developed, amounts of LSD 4 times as great as the doses to which the patients were tolerant were not as effective as the standard dose prior to chronic administration. Tolerance was completely lost 3 days after discontinuation of LSD.



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1144. Withdrawal symptoms in 'primary' meperidine addicts. H. ISBELL. *Natl. Inst. of Mental Health Addiction Research Ctr., PHS Hosp., Lexington, Ky.*

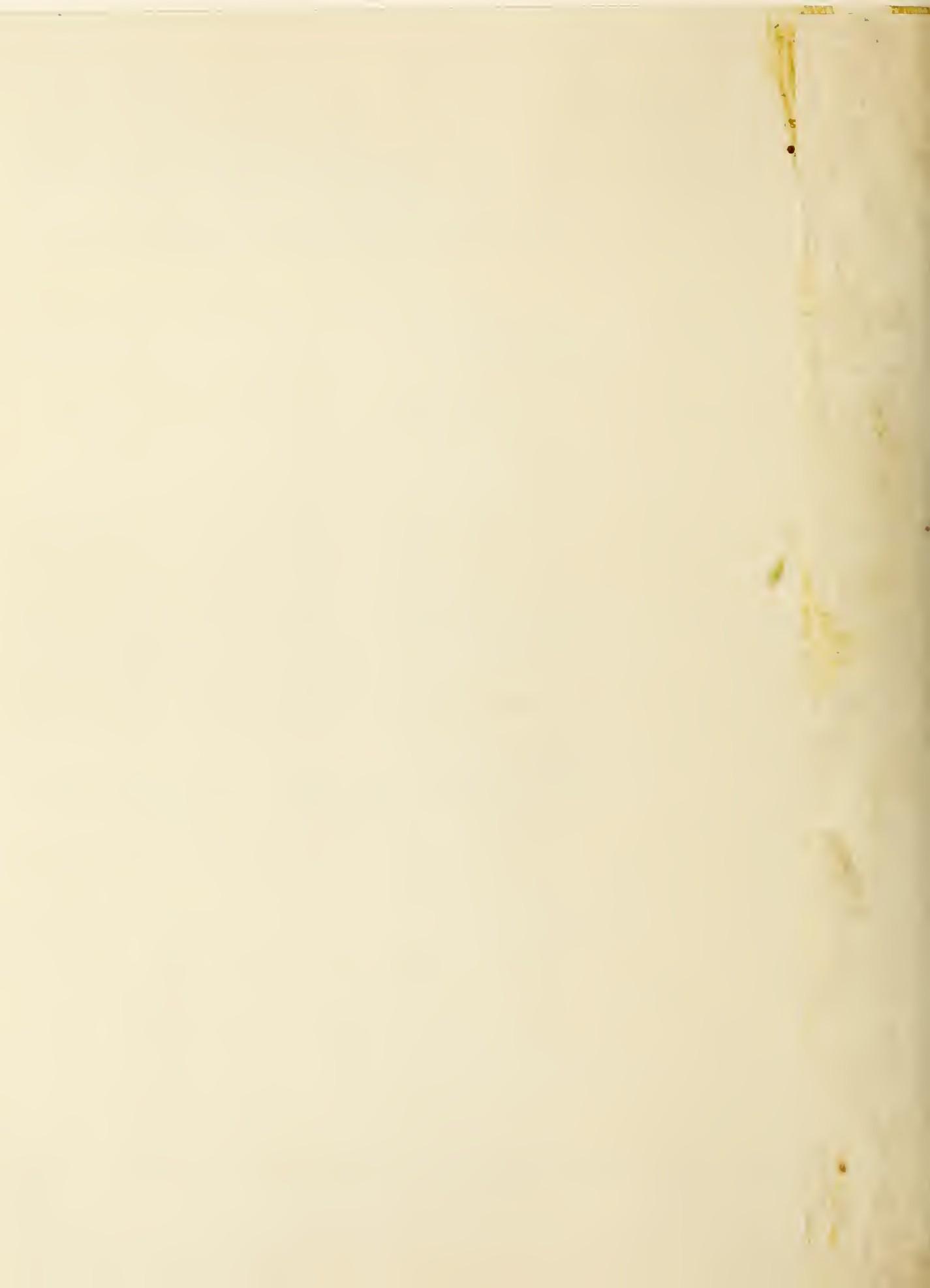
Four meperidine addicts, who had never been addicted to morphine ('primary' meperidine addicts) and whose histories were corroborated by their families or physicians, were stabilized on 1200-3200 mg of meperidine daily for 5-14 days. Nalorphine was ineffective in precipitating abstinence unless the stabilization dose of meperidine was 1600 mg daily, or more. Following abrupt withdrawal of meperidine, all 4 patients developed abstinence symptoms which differed from those observed after withdrawal of morphine in that signs of autonomic dysfunction were not as prominent, whereas restlessness and muscular twitching were more severe. Peak intensity of abstinence was reached in 7-12 hr. Objective symptoms disappeared rapidly in 3-5 days. Simultaneously, similar observations were made on 2 patients who were addicted to meperidine but who gave histories of having previously been addicted to morphine or codeine. The symptoms and course following withdrawal of meperidine from these 2 'secondary' addicts were identical with those observed in the 'primary' addicts. It is concluded that previous addiction to an opiate is not a necessary requisite for the development of physical dependence on meperidine.

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CHLORPROMAZINE AND RESERPINE: (a) Effects of each, and of combinations of each with morphine, (b) Failure of each in treatment of acute abstinence from morphine (Abstract). Fraser, H. F. and Isbell, H.; National Institute of Mental Health Addiction Research Center, Lexington, Ky.

Chlorpromazine (I) In a dose of 25 mg. i.m., or 50 mg. orally increased the intensity and duration of miotic and sedative effects of 10 and 30 mg. morphine sulfate (II) subcutaneously in postaddicts. I alone did not depress respiratory minute volume (RMV), and I plus II did not decrease RMV any more than II alone. Four patients stabilized on 240 mg. morphine daily were given, in one test, 800 mg. per day of I orally, and in another test, 100 mg. i.m. per day. I was given six hours prior to discontinuing morphine and it was continued at six-hour intervals for 36 hours after the last dose of morphine. I was of no value in treating acute symptoms of abstinence from morphine, since it was no better than a placebo treatment in the same patients.

Reserpine (III) In a single dose of 1 mg. seemed to potentiate the sedative effects of 30 mg. of morphine. III was not well tolerated by patients addicted to 240 mg. of morphine daily. III was of no value when given orally in a total dose of 3 mg. for the treatment of acute morphine abstinence symptoms. The first dose of 1 mg. was given six hours prior, the second dose concurrently with, and the third dose 14 hours after the last dose of morphine. These studies were conducted on 6 subjects, each of whom received placebo therapy for comparison.



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Quantitative comparison of the effects of chlorpromazine and pentobarbital on some autonomic responses.

J. R. Martin and J. L. Riehl (introduced by Klaus R. Unna) Department of Pharmacology, University of Illinois College of Medicine, Chicago 12

Chlorpromazine is reported to be an adrenergic blocking agent. We have conducted experiments on 26 unanesthetized, spinal, vagotomized cats in order to determine its potency as an adrenergic blocking agent. Chlorpromazine on slow i.v. administration produces a transient increase in systolic blood pressure and pulse pressure and a more persistent increase in pulse rate. Five to 10 minutes following the injection of the drug the blood pressure returns to control level and the pulse pressure decreases below the control level. Chlorpromazine in doses from 4 to 16 mg./kg. potentiated the chronotropic effect, the pressor response and the increase in pulse pressure produced by levarterenol (0.5-3 microgram./kg.). In addition the onset of the pressor response is delayed and the duration is prolonged. The blood pressure changes produced by the same amount of l-epinephrine are more variable than those produced by levarterenol. In our experiment we have found that chlorpromazine can potentiate or inhibit the rise in systolic blood pressure and the increase in pulse pressure produced by l-epinephrine. SY 28 (1 mg./kg.), used as a prototype for an adrenergic blocking agent, reduced the pressor response to levarterenol without affecting the pulse rate or pulse pressure. It reduced systolic pressure and increased pulse pressure following the administration of l-epinephrine.

It is difficult to reconcile these findings with an adrenergic blocking action of chlorpromazine since it intensifies all cardiovascular effects of levarterenol. Rather chlorpromazine appears to potentiate the inotropic, chronotropic, vasoconstrictor and vasodilator effects of these sympathomimetic amines in the spinal unanesthetized cat.

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Mailed in United States of America

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Vol. 15, No. 1, March, 1956

185. Prevention of barbiturate withdrawal convulsions in cats by cerebral electro-stimulation. C. F. ESSIG AND A. WIKLER.*
Natl Inst. of Mental Health, Addiction Research Ctr., PHS Hospital, Lexington, Ky.

Observation and continuous activity cage recording established the occurrence of 5-8 major convulsions during the first 5-10 days after abruptly withdrawing sodium barbital from each of 3 cats addicted to 475-895 mg/day for 67-182 days. In 2 cats addicted to 760 and 855 mg for 30 and 16 days respectively, no withdrawal convulsions occurred. Attempts to determine electro-convulsive seizure thresholds during the abstinence period appeared to prevent spontaneous barbital withdrawal convulsions. Thus no withdrawal seizures occurred in 4 cats which were stimulated twice daily after addiction to 380-760 mg for 47-146 days. Transdural stimulation of the hemispheres was delivered via implanted electrodes with biphasic pulses of 2 msec. duration, 200/sec. frequency for 5 sec. the strength of which was increased in 3-volt steps until convulsive movements occurred. One cat which had 14 spontaneous withdrawal seizures was readdicted on the same dose schedule to test the effect of electro-stimulation during abstinence. Electro-stimulation 3 times daily apparently prevented spontaneous abstinence seizures during withdrawal. Although, thus far, no electro-stimulated animal has had spontaneous barbital withdrawal convulsions, additional data relating dose and duration of addiction to convulsive expectancy are necessary.

EFFECTS OF CHLORPROMAZINE ON E.E.G.
AND ITS ACTIVATION. Edmund W. J. DeMaar
and W. R. Martin (introduced by K. R. Unna).
Dept. of Pharmacology, Univ. of Illinois, College
of Medicine, Chicago.

The effects of chlorpromazine on the E.E.G. and on its activation by auditory stimulation and by epinephrine were studied in 40 unanesthetized cats whose spinal cords were transected at C 1. In 36 of these preparations chlorpromazine in doses of 1.5 or 10 mg/kg produced a diminution of low amplitude high frequency activity. The resulting records of slow activity contained 1-3 cycles per sec. waves, 8-12 cycles per sec. spindles and 7-10 cycles per sec. waves, that have a slower ascending phase than the sleep spindles. In some preparations a transient period of activation of 1-2 min. duration was seen within the first 10 min. following injection of chlorpromazine. The decrease in frequency and the degree of spindling did not appear to be correlated to the dose. In 30% of the preparations chlorpromazine failed to suppress the activation of the E.E.G. by auditory stimulation. Activation of the E.E.G. was obtained in 50% of the preparations by epinephrine in doses from .5 to 3 μ g/kg. With repeated injections of epinephrine the activation became increasingly feeble and the injections were followed by increasing appearance of spindles. In 25% of our preparations chlorpromazine failed to block the activation by epinephrine. Administration of norepinephrine in doses from .5 to 3 μ g/kg did not produce activation. After repeated administrations it causes slowing of the E.E.G. and the appearance of 8-12 cycles per sec. spindles. These effects of norepinephrine become more pronounced following the administration of chlorpromazine. (This study was supported in part by research Grant 983 of the PHS).

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Reprinted from FEDERATION PROCEEDINGS
Vol. 15, No. 1, March, 1956

1377. Minimum dose of barbiturates required to produce physical dependence. H. F. FRAZER, HARRIS ISBELL, A. WIKLER, R. E. BELLEVILLE, C. F. ESSIG AND H. E. HILL. Natl. Inst. of Mental Health, Addiction Research Ctr., PHS Hosp., Lexington, Ky.

Twenty-three partially tolerant patients received either 0.8 or 0.6 gm of secobarbital daily for 42-120 days. When the drug was withdrawn abruptly 1 of 5 receiving 0.8 gm and 2 of 18 receiving 0.6 gm daily had grand mal convulsions; none developed delirium. In another experiment, 10 nontolerant subjects received 0.4 gm secobarbital and 8 nontolerant patients received 0.4 gm pentobarbital daily. All were observed for 30 days prior to, 90 days during and 45 days after, drug administration. Results with 0.4 gm secobarbital and with 0.4 gm pentobarbital were similar. Initially, 16 of these 18 subjects showed marked, and 2 showed mild intoxication (incoordination, dysarthria, confusion, poor judgment and various mood changes). These changes subsided rapidly from the 4th through the 7th day of drug administration. After 80 days of drug intake there was no significant impairment of function as judged by performance tests (coordination, reaction-time and pursuit rotor). After abrupt withdrawal of barbiturates none of these 18 subjects given 0.4 gm developed convulsions or delirium; they showed only transient tremor and/or mild anxiety with insomnia. One showed frequent bursts of high voltage slow waves in EEG. Following withdrawal of 0.2 gm secobarbital from 2 subjects who had received it nightly for a year, no significant symptoms were observed. Conclusion: in healthy males, a chronic dose of greater than 0.4 gm secobarbital or pentobarbital daily is required to produce a clinically significant degree of physical dependence.

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Reprinted from FEDERATION PROCEEDINGS
Vol. 15, No. 1, March, 1956

1378. Addictive potentialities of hexamethyl-
eneimines. H. F. FRASER. *Natl. Inst. of Mental
Health, Addiction Research Ctr., PHS Hosp.,
Lexington, Ky.*

Neither objective signs nor subjective symptoms of morphine-like effect were observed in non-tolerant former addicts after administration of the following compounds: 1-methyl-4-phenyl-4-carbethoxy hexamethyleneimine (I) in doses of 25-150 mg s.c. or 50-300 mg orally; 1,3-Dimethyl-4-phenyl-4-carbethoxy hexamethyleneimine (II) in doses of 5-200 mg s.c.; and 1,2-Dimethyl-4-phenyl-4-carbimethoxy-hexamethyleneimine (III) in doses of 5-80 mg s.c. or 40-100 mg orally. *Dl*-alpha-1,3-Dimethyl-4-phenyl-4-propionoxy-hexamethyleneimine (IV) in doses of 75-150 mg induced objective signs and subjective symptoms of morphine-like effect roughly equivalent to those which follow 15-30 mg of morphine but of shorter duration. I, II and III in doses of 100, 150 and 150 mg s.c. every 4-6 hr. were ineffective in suppressing symptoms of abstinence in patients who were addicted to 240-280 mg of morphine daily. All addicted patients who received multiple doses of I, II and III developed nervousness, insomnia, twitches and tremors which persisted for 12-24 hr. after the drugs were discontinued. One addicted patient developed signs of vascular collapse and pulmonary edema after receiving 150 mg of I. Similar but milder episodes occurred in 2 other patients. Two hundred mg of IV every 3 hr. suppressed abstinence completely and no toxic symptoms were observed. Addictive potentialities of I, II and III are either low or nonexistent; complete evaluation, however, was impossible because of the central nervous system excitation and other toxic effects induced by these drugs. IV, on the other hand, has addiction liability at least equal to that of meperidine and approaching that of morphine.

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Feb. 1, 1961, March, 1961

1479. Attempted addiction to morphine.
Human Islet. Natl. Inst. of Mental Health,
Addiction Research Ctr., P.H.S. Hosp., Lexington,
Ky.

In both nonaddict former addicts and nonaddict nonaddicts morphine spontaneously in doses of 5-10 mg (nonaddicts) or 10-20 mg (former addicts) caused subjective sensations of dizziness, light-headedness, tremors, warmth, dimness in speech, partial amnesia, uninhibited behavior, nausea and, in some cases, vomiting. Such effects disappeared in less than 1 hr. and were succeeded by drowsiness and sleep. Former addicts disliked the drug. With the higher doses confusion and visual hallucinations occurred in some former addicts. Objectively, morphine reduced body temperature, depressed respiratory minute volume and caused slight pupillary constriction. Six former addicts were given 10 mg of morphine every 4 hr., increasing in 14 days to 16-35 mg every 4 hr. Two patients withdrew from the experiment because of hallucinations. The other 4 continued but would not permit elevation of the dose above 100-130 mg daily. Hallucinations disappeared after 2 wk. No definite symptoms were observed after abrupt withdrawal of morphine after 21 days' addiction. Four other addicts received morphine in doses increasing to 7-12 mg every 4 hr. for 26-31 days and 1 patient received morphine in doses increasing to 9 mg every 3 hr. for 42 days. Disagreeable side effects were less with such small doses more frequently administered but again patients disliked medication. No definite symptoms of abstinence occurred following withdrawal in these last 5 men. Addiction liability of morphine is low or nonexistent.

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Made in United States of America

Reprinted from *Proceedings Paracelsus*
Vol. 14 No. 1 Maria, 1961

144. Effect of chlorpromazine, reserpine and
'Frenquel' on LSD reaction. HAZAR ISRAEL
Nat'l Inst. of Mental Health, Addiction Research
Ctr., PHS H-30 Lexington, Ky.

It was hoped that blocking or reversal of psychoses induced by the diethylamide of lysergic acid-LSD-2F could be used as a screen for predicting clinical usefulness of new tranquilizing agents. Intensity of LSD reaction was evaluated by a questionnaire and a short mental status examination supplemented by measurements of pupillary size, knee jerks and blood pressure. All experiments were double-blind and included in the same pairs of combinations in random order of LSD-2F, chlorpromazine-placebo, LSD-tranquillizer-placebo, LSD placebo-tranquillizer and LSD-tranquillizer. In 5 experiments using 39 patients in which 50-100 mg of chlorpromazine was given 30 min prior to 40-60 µg LSD, a strong but not always significant trend to reduction in the intensity of the reaction was observed. Seventy-five mg of chlorpromazine orally 1½ hr. after 60 µg LSD did not reduce the intensity of the LSD reaction whereas 25 mg i.m. did reduce its intensity. One mg of reserpine orally 10 and 2 hr. before or 2.5 mg orally 22, 10 and 2 hr. before 60 µg LSD did not reduce the intensity of the LSD response. Two mg of reserpine intramuscularly 22, 10 and 2 hr. before LSD intensified the LSD reaction. Twenty mg of 4-piperidyl-diisopropyl-carbinol (Frenquel) i.v. for 7 days prior to 60 µg LSD had no effect. Sixty mg of Frenquel i.v. and 40 mg i.v. 2 and 3 hr. after 100-200 µg LSD also failed to influence the reaction. Because of the results with reserpine, the LSD reaction is not an effective screen for detecting tranquilizers.

EFFECT OF CHLORPROMAZINE ON CARDIOVASCULAR
RESPONSES TO EPINEPHRINE AND NOREPINEPHRINE IN
THE CAT. W. R. Martin. Dept. of Pharmacology, Univ. of
Illinois College of Medicine, Chicago, Illinois.

It was previously reported that chlorpromazine potentiated the inotropic, chronotropic and pressor effects of norepinephrine and could either depress or potentiate the effect of l-epinephrine. In order to further study the difference between the effects that chlorpromazine exerts on the vascular responses to epinephrine and norepinephrine a fixed dose of norepinephrine (.5-1.0 ug/kg) or epinephrine (1.0-2.0 ug/kg) was administered at 10-min. intervals before and after the administration of chlorpromazine to spinal vagotomized cats. Chlorpromazine enhanced and prolonged the pressor response evoked by norepinephrine. As a measure of the prolongation of the pressor response to norepinephrine, the Decay Time 50 (the time necessary for the pressor response to return to a value midway between the control systolic pressure and the peak systolic pressure) of all pressor responses was determined. A prolongation of the effects of norepinephrine by 60-500% was observed within 5 min. after the administration of chlorpromazine (5.0-10.0 mg/kg). Two hr. after the administration of chlorpromazine the effect of norepinephrine was still prolonged by at least 30%. In contrast to its effect on norepinephrine,

THE CAT. W. B. Muller, Dept. of Zoology, University of Michigan, Ann Arbor.

of the present investigation is to determine the effect of the various organic acids on the growth of *Chlorobium* and *Thrixosphaera*. A brief account of the methods used is given below.

The cultures were grown in 100 ml. Erlenmeyer flasks containing 20 ml. of the following medium:

Glucose 10 g., yeast extract 1 g., peptone 1 g., NaCl 0.5 g., K₂HPO₄ 0.1 g., MgSO₄ 0.1 g., MnSO₄ 0.01 g., FeSO₄ 0.01 g., CuSO₄ 0.001 g., HgCl₂ 0.001 g., and 0.01% agar. The flasks were sterilized at 120° C. for 15 min. and cooled in an inverted position. After cooling, 1 ml. of a culture of *Chlorobium* or *Thrixosphaera* was added to each flask. The flasks were then placed in a dark incubator at 28° C. and the cultures were examined daily for growth.

The growth of *Chlorobium* was measured by counting the number of colonies per ml. of culture. The growth of *Thrixosphaera* was measured by counting the number of spores per ml. of culture. The results are shown in Table I.

As can be seen from Table I, the growth of both *Chlorobium* and *Thrixosphaera* is inhibited by the presence of organic acids. The inhibition is more pronounced with *Chlorobium* than with *Thrixosphaera*. The inhibition is dose-dependent, with the growth being inhibited more at higher concentrations of the organic acids.

chlorpromazine (1, 5 and 10 mg/kg) decreased or reversed the pressor response to epinephrine in 11 of 12 cats. The action of chlorpromazine on the vascular response to epinephrine resembles that of an adrenergic blocking agent such as Dibenzyline. However the action of chlorpromazine on the vasomotor reaction of norepinephrine cannot be explained by adrenergic blockade. The possibility that chlorpromazine interferes with the metabolism of sympathomimetic amines will be discussed. (This study was supported in part by Research Grant 983 of the Public Health Service.)

ent purposes to ascertain if you can find any information
to corroborate the statement made by Mr. Smith concerning
the conduct of the officers of the State of New York in their
relations with the Indians. You will also have the power to
review all the documents in your possession which relate to
the Indians, particularly those concerning the actions of the
State. You will also have the power to inspect all the
records and documents of the State of New York relating
to the Indians, and to make such examination of them as
you may think necessary. You will also have the power to
make such investigation as you may think necessary of
the conduct of the officers of the State of New York in their
relations with the Indians.

(Continued)

The Search for a Non-addicting Analgesic

By Harris Isbell, M.D.

From the Addiction Research Center, Public Health Service Hospital, Lexington, Kentucky *

Since potent analgesics are indispensable in clinical practice and at the same time constitute a danger because of their addiction-producing properties, a drug has long been sought which would be non-addicting and at the same time combine the following properties : analgesic potency equal to that of morphine; toxicity no greater and, if possible, less than that of morphine; no undesirable side effects; and at the same time no tolerance to the pain-relieving effect.

Such a substance has been sought since 1929 under the aegis of the Committee on Drug Addiction and Narcotics of the National Research Council. The first approach was to modify the molecule of morphine. This effort shifted to the synthetics with the discovery of pethidine and methadone. In the last few years emphasis has shifted to the analgesic properties of nalorphine and mixtures of opiates and nalorphine. Although nalorphine is itself a modification of morphine, it is an opiate antagonist and has quite different properties. For the time being, the object of this search has not been attained; analgesic potency and addiction liability seem to equal each other.

Six groups of analgesics are known : the morphine, morphinan, pethidine, hexamethylenecinuine, methadone, and dithienylbutenylamine families. It is possible, with some imagination, to make out in all six families a central phenylpiperidine nucleus, and it may be that such a structure is

necessary for analgesia but is always associated with physical dependence. Such a gloomy view is not necessarily justified. The synthetic analgesics have been discovered, either by preparing a new compound with a structure similar to a drug already known, or by a synthesis made for some purpose other than analgesia. In the latter case, routine testing disclosed that the drug in question induced morphine-like effects in mice and in other animals. Thus new drugs were discovered by their pharmacological resemblance to morphine. Therefore it seems that a new approach could be found : drugs with the phenylpiperidine structure and drugs giving morphine-like effects in lower animals should be avoided and an agent should be looked for which would be analgesic without being otherwise morphine-like; one difficulty in this approach is that it is not easy to deduce the effect on subjective reaction to pain in patients from the analgesic effect in lower animals. It may be that a number of promising drugs have already been discarded because of only weak analgesia in animals; an example of what is meant is nalorphine, which is a very weak analgesic in animal tests but is as effective as morphine in relieving post-operative pain.

Nalorphine does not create physical dependence, but it has undesirable side effects (disturbed mental reactions). Furthermore, it is not known whether tolerance to its analgesic effects would develop with continued use. Investigations are currently under way on possible modifications of the nalorphine structure, which might reduce the side effects while retaining the analgesic effects and the lack of addiction liability.

* The present note summarizes, by permission of the author, a paper he published in the *Journal of the American Medical Association*, 161 : (13) 1254 (July 28) 1956.

Khat

Khat is a shrub the leaves of which are used as a stimulant or a medicine in certain regions of East Africa and Arabia. The question of khat has been placed by the Narcotics Commission on the provisional agenda of its twelfth session, scheduled to meet in April 1957, on the proposal of the representative of Egypt. The following article is a compilation of information from existing published sources on the subject, which are of varying degrees of authority; and it should be regarded as of a background character, pending closer examination of the question by the Commission.

Historical Background

Khat was probably known and used on the Ethiopian uplands, where it seems that it originated, in very ancient times. It is, however, impossible to fix accurately its original habitat and the region where it first developed. As is usual in such cases, some authors state that it was not unknown to classical antiquity. Merab, for instance (58), thinks that it was the smoke of khat that inspired the Delphic pythoness, that Homer's *nepenthe* offered by Helen to Telemachus was none other than khat and that Alexander the Great used it to cure his army of an epidemic disease. There are equally unverifiable suggestions with regard to cannabis and opium, and no importance can be attached to such suppositions.

The first historical reference, as far as could be determined from the literature consulted, occurs in a medieval Arab manuscript (MS.143, Bibliothèque nationale, Paris), where it is stated that the King of Ifat, Sabr Ad-Din decided to plant khat in the town of Marad (the period in question seems to be the first half of the fourteenth century). According to Rochet d'Héricourt (75), khat was introduced from Ethiopia into the Yemen in 1424 by Sheikh Abu Zerbin. Another reference to its cultivation in the fourteenth century in the region of Aden and in the Yemen is found in a sixteenth-century Arab chronicler, Abdul-Kadir. Its cultivation in that region is thought to be earlier than that of coffee (82). Khat was not known to the scientific world until the end of the eighteenth century. During an expedition organized by King Frederick V of Denmark, the physician and botanist Peter Forsskal collected, among many other plants, specimens of khat, which he described under the name of *Catha edulis*. The only survivor of the five members of the expedition, the Hanoverian geographer, Karsten Niebuhr, published the botanical papers in 1775, and in memory of his friend called *Catha edulis* "Catha edulis forssk" (65).

In the first half of the nineteenth century, various travellers and scientists visiting Arabia and East and South East Africa referred to and described khat either under that name or variants of it : *Celastrus edulis* Vahl, by Ferret and Galinier (37), *Catha Forsskali A. Richard*, by R. Petit, *Methyscophyllum glaucum*, by Ecklen and Zeyher (27), etc.

Description

Khat is a shrub with persistent leaves of the Celastraceae family, relatively of little importance, which includes the spindle-tree, *Celastrus*, etc.; mention may be made, however, of a Philippines plant of the same family, *Lophopetalum toxicum*, containing a poisonous substance lophopetalin, which is used in the composition of arrow-head poisons (67). Khat grows to between 3 ft and 6 ft (1-2 m) in high and dry soils, reaches 20 ft (6 m) on the moist slopes of the Ethiopian mountains

and may even in the equatorial region under favourable circumstances reach a height of 80 ft (25 m). The trunk may be some 24 in (60 cm) in circumference and the bark is thin, smooth and brown; in appearance the tree is not unlike the tea shrub.

The new leaves are reddish-brown, becoming greenish-yellow when fully grown. They are bifarious, elliptical, lanceolate, sharp, coriaceous and almost tasteless. Dimensions vary widely from 0.2 in (0.5 cm) to almost 3 in (7 cm). The limb, which at the base is smooth, has over the remainder of the leaf short, mossy serrations; the median vein projects on the under, reddish side; the secondary veins meet before the margin of the limb; between the secondary veins the smaller ones form a reticulate venation. From the histological point of view, Perrot (67) gives the following description : "Glabrous epidermis; bi-facial mesophyl with two palisade layers and spongy parenchyma with ramous cells of twin crystals, isolated or sometimes grouped in clusters in the same cell. Fasciculate system in an arc almost closed by two superior phloem-lignous strands. Many periphloem units. Crystalline phloem".

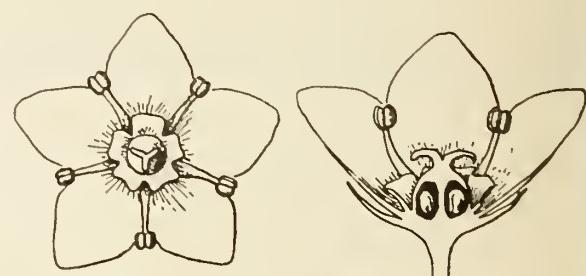


FIGURE 1
Flower of khat

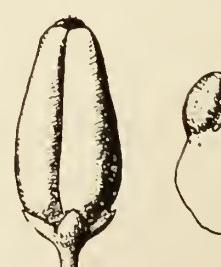


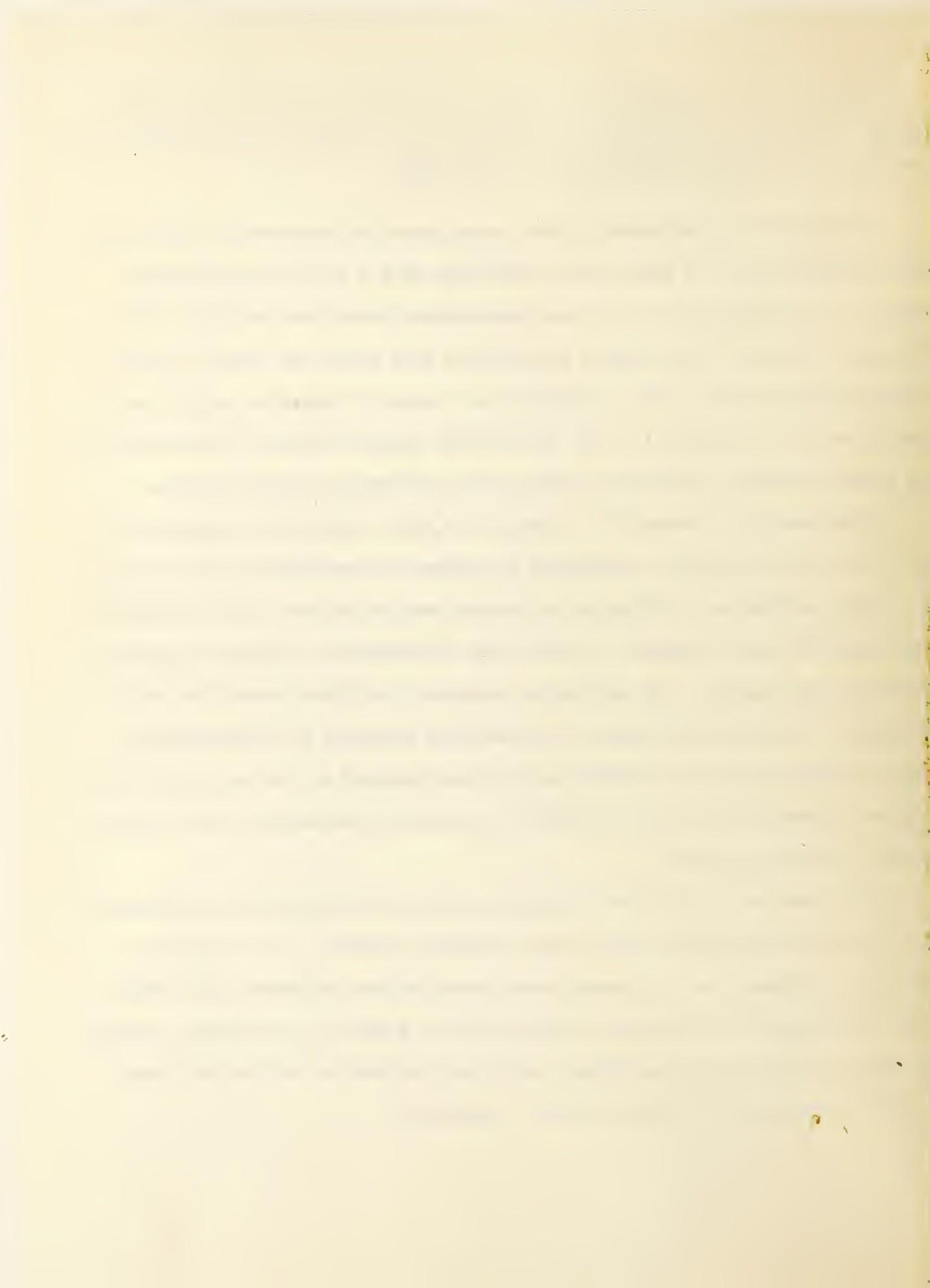
FIGURE 2
Fruit and seed of khat (note the "wing" of the seed)

J. R. JASPER AND K. L. UPTON, UNIVERSITY OF ILLINOIS
DEPARTMENT OF MEDICAL PHYSIOLOGY, THE EFFECTS OF CHLORPROMAZINE ON
THE ACTIVATION OF THE CEREBRAL CORTEX AND THE CORTEX AND BULBAR RETICULAR FORMATION
AT THE CONGRES INTERNATIONAL DE PHYSIOLOGIE.

The effects of chlorpromazine were investigated in unanesthetized cats which were paralysed either by spinal cord transection at C.I or by succinylcholine injection. The control E.E.G. of these preparations showed low amplitude, high frequency activity. In the spinal preparations 8-12 cycles per second spindles occasionally appeared. Action potentials were evoked by single or paired shocks (delay from 20 to 220 msec.) to the ipsilateral sciatic nerve and were recorded in the bulbar reticular formation of preparations paralysed by succinylcholine.

Chlorpromazine in doses of 1, 5 and 10 mgm./kgm. produced the appearance in the E.E.G. of slow activity, containing 1-3 cycles per second waves, 8-12 cycles per second spindles and 7-10 cycles per second waves which have a slow ascending phase than the sleep spindles. In 50% of the preparations a transient period of activation was observed. The activating response to auditory stimulation or to epinephrine (0.5-1 microgram./kgm.) was slowed and depressed by chlorpromazine. After the administration of chlorpromazine there appeared at the beginning of the auditory activating stimulus or following the shock to the sciatic nerve a large diffuse cortical potential.

Chlorpromazine at the 5 or 10 mgm./kgm. dose level increased the amplitude of the first evoked potential in the bulbar reticular formation. The refractory period was prolonged, as the second evoked potential was decreased, when evoked with a delay period of 100 msec. Pentobarbital in a dose of 15 mgm./kgm. administered after chlorpromazine completely abolished the first as well as the second evoked potential in the bulbar reticular formation.



DEMONSTRATION OF THE ANTICONVULSANT (ANTI-EPILEPTIC)
ACTION OF CHLORPROPAMIDE

J. S. F. Bailey and Med. Center

Alcohol Addiction Research Center, PGH Hospital, Lexington, Ky.

An attempt was made to obtain a chlorpropamide induced convulsion-like syndrome in a Rhesus monkey. Unexpectedly, a major convolution was observed. Three more monkeys were given the drug under better controlled conditions, to confirm the observation. An activity cage which recorded the incidence of major convolution on a continuous basis was used. Convulsions did not occur during 8 to 11 day interval before drug administration. Convulsions were not recorded during a 6 to 12 day period when 85 mg./kg. of the drug were given orally once daily. The daily dose was then increased to 42 mg./kg. in one animal, 7 mg./kg. in 2 animals, and 77 mg./kg. in one animal. All 4 animals had from 8 to 13 major convulsions while on the chlorpropamide regime. The seizures occurred spontaneously, or could be induced (sometimes) by chasing the animal. Transient tonic seizures and myoclonic jerks were also noted. All convulsions occurred during drug administration. The longest time interval between the final dose of drug and the last major seizure was 12 hours. Withdrawal seizures were not observed. During inter-seizure periods the animals were

(Presented at Meeting of Am. Soc. Pharmacol. & Exper., Chicago, Illinois 15-19 April 1956).



Appropriate cautionary statement or advice: Transitory hallucinations
occurred in 30 (reset 3 of the animal) sometime
during the period when seizures occurred. The extrapolation
of animal data to man is not intended, but reasonable caution
in use of large doses of the drug may be indicated in epileptics
or by the carbamate and alcohol withdrawal.



Pyruvate and its derivatives have been shown to exert a variety of pharmacological effects. These include anticonvulsant, analgesic, anti-inflammatory, and hypotensive properties. Pyruvate, chloropyruvic acid, hydroxypropanoic acid, bromopyruvic acid, and substituted pyruvates induce muscarinic effects in mice and man, and mice following intravenous or intraperitoneal administration of 200-500 mg./kg. The initial muscarinic effects are followed by cardiovascular effects and death of the animal within 12 hours. While the muscarinic actions are antagonized by atropine, the lethality is not altered. The mechanism of the conversion of these substances was investigated. Since it seemed possible that the substituted pyruvate might be metabolized to substituted acetylcholinium, fluorescamine, and chloroacetylcholine were synthesized and were found to exhibit muscarinic effects. Fluoropyruvic acid, chloropyruvic acid, fluorescamine, and chloroacetylcholine did not significantly inhibit the rate of oxidation of acetylcholine by purified bovine erythrocyte cholinesterase. One of the active derivatives of pyruvate inhibits oxidation of pyruvate and other substrates, kidney, and brain homogenates in systems fortified with ATP. At 0.01 M, olive pyruvate inhibited oxidation of succinate, glutarate, and citrate at a concentration of 0.05 M. These data are consistent with the hypothesis that the muscarinic effects are related to formation of substituted acetylcholinium. The inhibition is related to inhibition of carbohydrate oxidation.



Substitution of alcohol for barbiturates in chronically
intoxicated patients. Green, H. F., Isbell, H., Wikler, A.,
and Jokinen, A. J. National Institute of Mental Health
Addiction Research Center, Lexington, Kentucky.

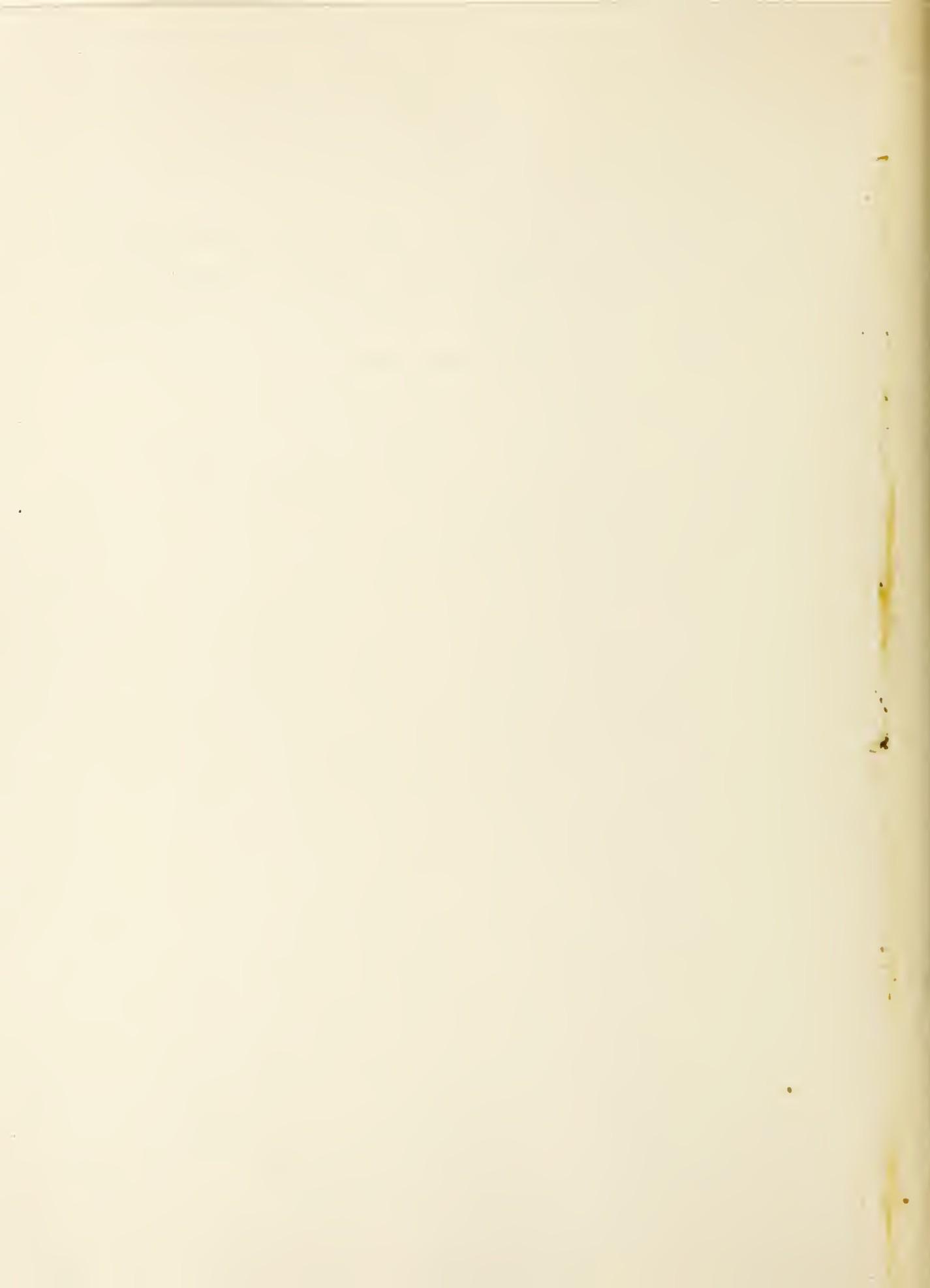
Objective was to determine the degree of pharmacological equivalence of barbiturates and alcohol with respect to their physical dependence-sustaining properties. Nine patients, 7 of whom were addicted to barbiturates on admission, were chronically intoxicated for 39 to 44 days with pentobarbital (1.07 to 2.3 grams daily) or secobarbital (1.06 to 1.96 grams daily) in the highest dosage compatible with safe ambulatory management. In 3 patients, pentobarbital was smoothly substituted for secobarbital for seven days, after which they were returned to secobarbital without incident. Barbiturates were abruptly discontinued in all patients and 95 per cent ethyl alcohol, in daily dosages ranging from 282 to 460 ml., was substituted for the barbiturates for 14 days and then discontinued abruptly. During substitution of alcohol, 3 patients had one grand mal convolution and a delirium lasting one or two days. Convulsions appeared 168, 176 and 232 hours after last dose of barbiturates. Following withdrawal of alcohol each of 3 patients had one grand mal convolution and 2 of these had a delirium lasting two days. Convulsions

NIMH-ARC-Lex, Ky.
(2-20-57)

J. Pharmacol. & Exper. Therap. 119: 21-40 (1957)

appeared 13, 25 and 82 hours after alcohol was discontinued. On the basis of previous studies (Arch. Neurol. & Psychiat., 64: 34, 1952) a definitely higher incidence of convulsions and delirium would be expected following abrupt withdrawal of barbiturates at such dosage levels without treatment.

Conclusion: Substitution of alcohol for pentobarbital or secobarbital partially suppresses and otherwise modifies the barbiturate abstinence syndrome.

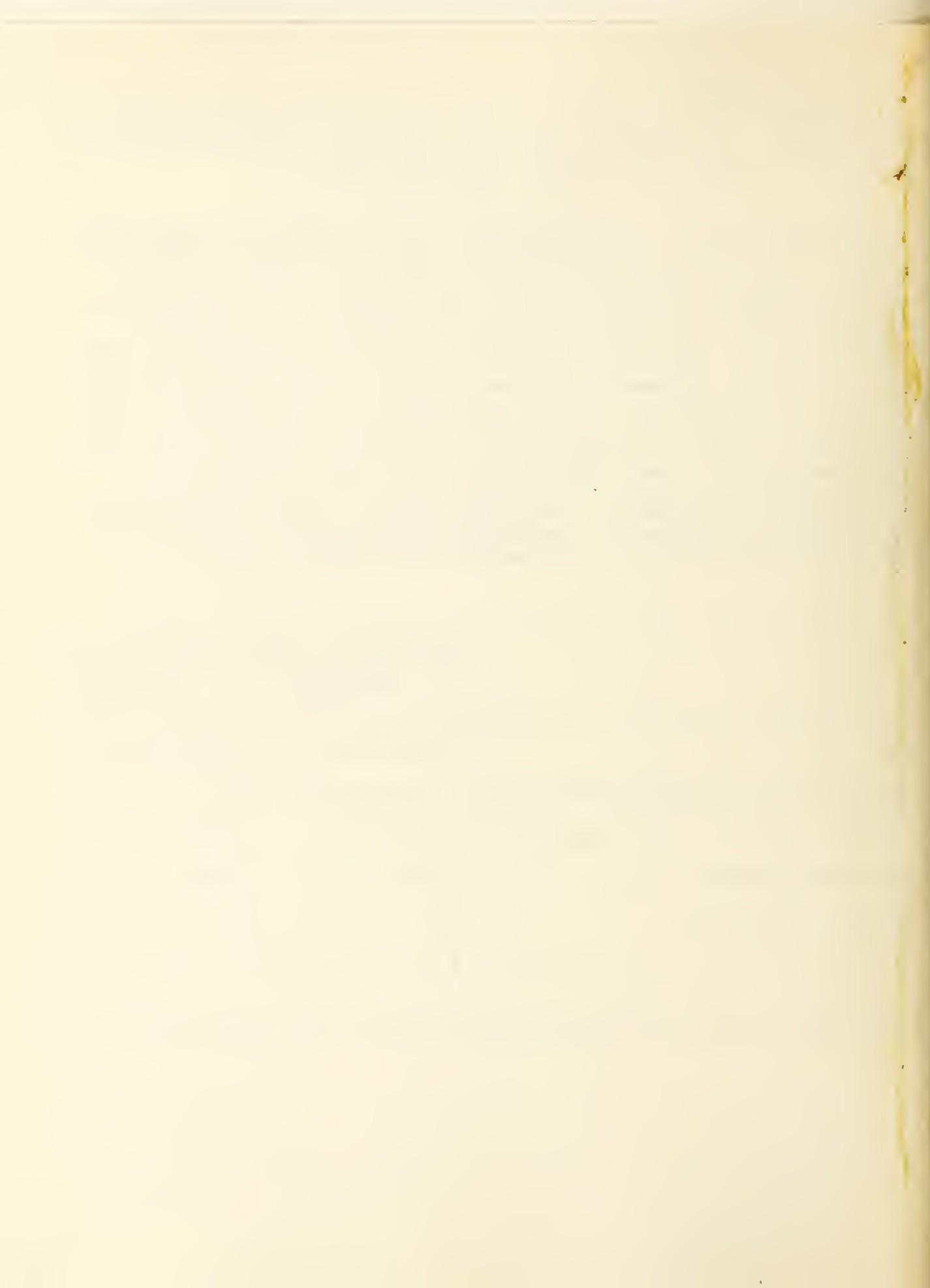


JOURNAL OF PHARMACOLOGY AND CENTRAL NERVOUS SYSTEM EFFECTS PRODUCED BY HALOGENATED PYRUVIC ACIDS. C. R. Martin, H. Bogen, W. L. Nyhan and D. H. Abdulian (introduced by K. M. Thrall). Jour. of Pharmacology, Univ. of Illinois College of Medicine, Chicago, J. Pharmacol. Exp. Therap., 119(1), 165, 1957.

The effects of chloro- and bromopyruvic acid were studied in cats and mice with particular reference to the sequence of their occurrence. The early effects of chloro- and bromopyruvic acid begin within one minute following intravenous injection, often persist for more than ten minutes, and include lacrimation, salivation, increased gastrointestinal motility, urination, a rise in blood pressure, body movements above and below the level of section in the spinal cat, inhibition of the patellar reflex, activation of the EEG and short lasting analgesia. Salivation, lacrimation, increased gastrointestinal motility, and activation of the EEG are depressed by atropine but not by hexamethonium while inhibition of the patellar reflex is further depressed by atropine. Atropine neither enhances nor depresses the analgesic potency of bromopyruvic acid in mice. With larger doses of chloro- and bromopyruvic acid this initial phase is followed by a normal bradycardia, a gradual but progressive fall in blood pressure, and a decreased sensitivity of the cardiovascular system to the pressor effects of epinephrine and norepinephrine. The patellar reflex is gradually depressed and becomes isolectric. A comparison of relative potency of chloro- and bromopyruvic acid made in mice is summarized in the following table:

	Bromopyruvic Acid mgm./kgm.	Chloropyruvic Acid mgm./kgm.
LD ₅₀	72(65.5-79.5)	204(190-216)
Analgesic (? min. after injection) Dose 50	17.5(11.4-26.8)	64
Analgesic (5 min. after injection) Dose 50	49(31-77.3)	62(40.8-94.2)
Salivation (Threshold)	50-10	20-40
Lacrimation (Threshold)	10	40

(This study was supported by Research Grant 983 of the Public Health Service.)



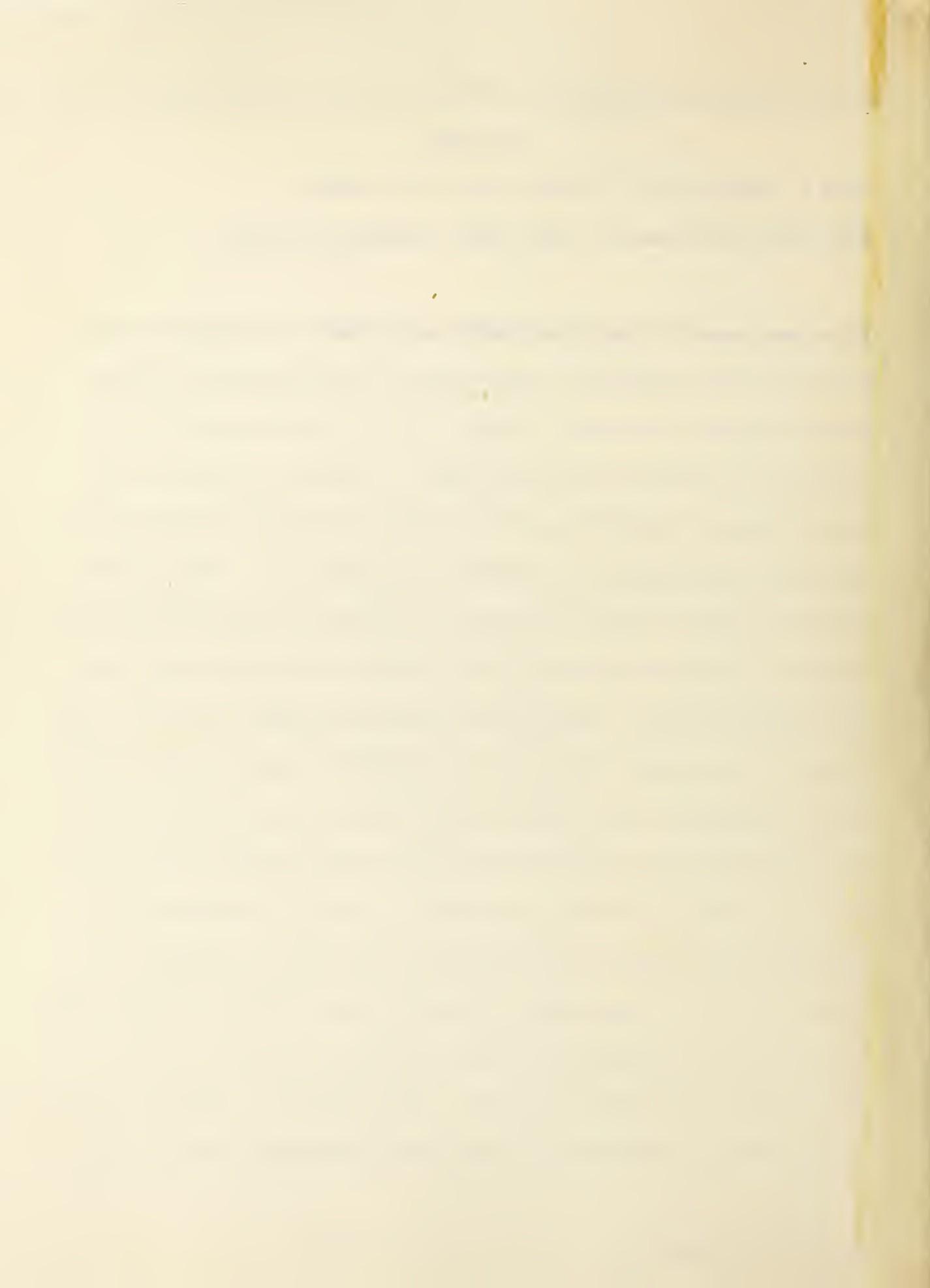
PLASMA AND URINARY CORTICOIDS DURING A CYCLE OF MORPHINE ADDICTION

(Abstract)

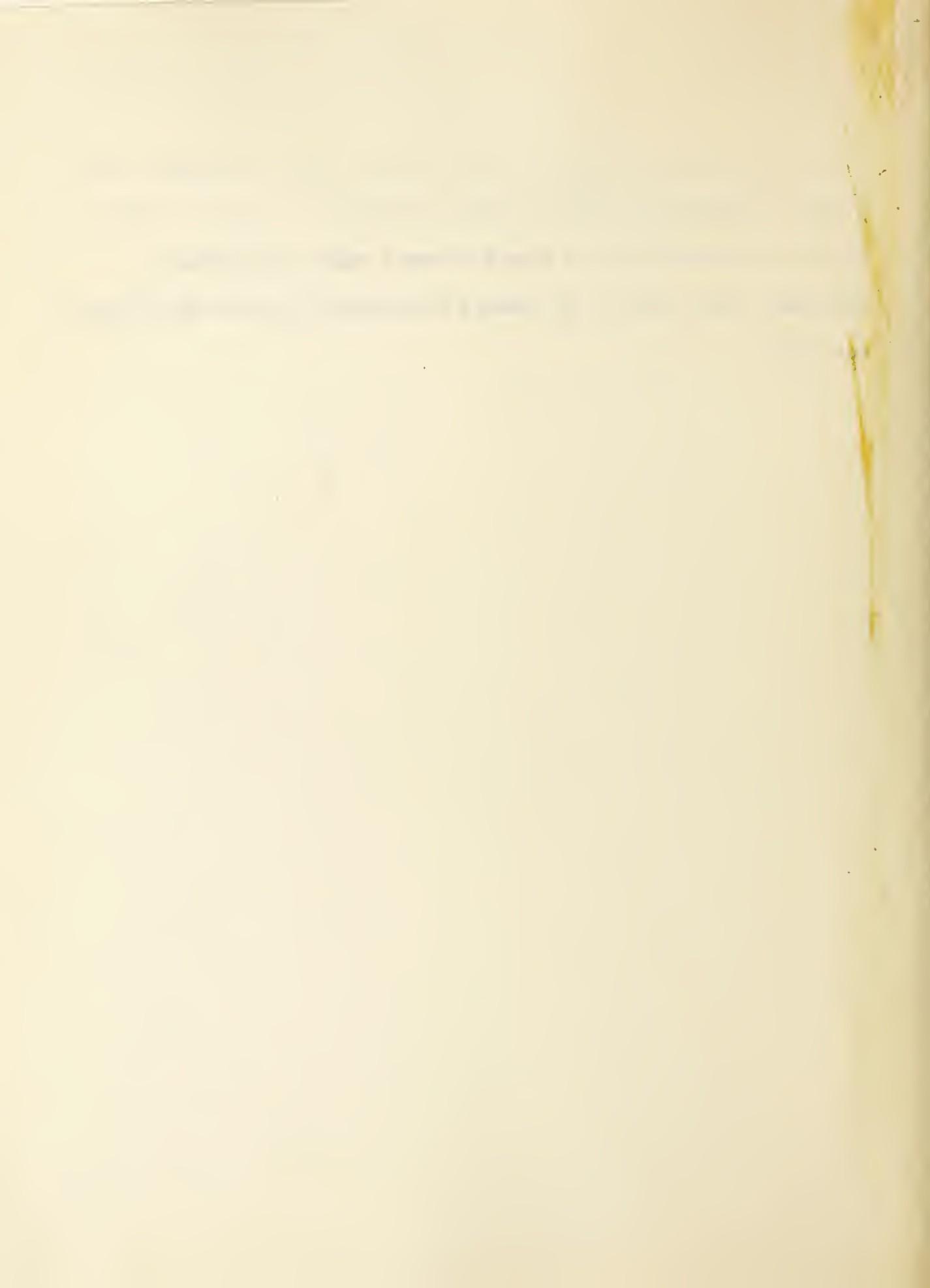
Anne J. Eisenman, H. F. Fraser, and J. W. Brooks

NIMH Addiction Research Center, PHS, Lexington, Kentucky

Urine and plasma 17-hydroxycorticoids were studied on 2 subjects during a cycle of morphine addiction: control period, 40 days; addiction, 60 days; abrupt withdrawal; recovery, 50 days. ACTH or hydrocortisone was administered at least once during each phase. Placebos were given several times during the preaddiction period. Urinary and plasma corticoids were decreased during addiction, increased during withdrawal. Administration of ACTH resulted, within 2 to 3 hours, in a decrease to zero of blood eosinophils and in about the same high level of plasma corticoids during control and addiction periods. The response of urinary corticoids was less, but the increases were similar during control and addiction phases. After infusion of hydrocortisone (2.5 mg. per kilo body weight), its rate of disappearance from the plasma was not significantly altered during addiction as compared to control periods. In these loading tests the amount of hydrocortisone excreted during 24 hours was comparable during control, addiction, and recovery periods. These results indicate that the catabolism of the hormone is not altered during addiction. Withdrawal was accompanied by a striking rise in plasma and urinary corticoids. The peak plasma corticoids appeared at about 36 hours, the excretion peak on the second day. In several other



subjects with more prolonged addiction to higher doses of morphine, much greater and earlier increases in plasma corticoids were noted. Administration of morphine 48 hours after withdrawal relieved symptoms of abstinence within 4 hours and caused a concurrent precipitate fall of plasma corticoids.



EFFECTS OF INTERNEURON DEPRESSANTS ON INHIBITION AND FACILITATION OF THE
PATELLAR REFLEX. D. H. Abdulian,* W. R. Martin* and K. R. Unna. Dept. of
Pharmacology, Univ. of Illinois College of Medicine, Chicago. Fed. Proc. 16:1,
277, 1957.

Recent work (Eccles, 1956) has indicated that ipsilateral inhibition of the patellar reflex may involve an interneurone. For this reason, it was decided to reinvestigate the effects of interneurone depressants on spinal inhibition. The patellar reflex was elicited once every second with a tapping hammer in the unanesthetized spinal cat and was recorded on an ink writing kymograph. The central ends of cut ipsilateral and contralateral sciatic nerves were stimulated for a 5 sec interval every minute with graded stimuli. The degree of facilitation and inhibition was expressed as percentage of the mean control patellar reflex height and this value was plotted against stimulus strength on arithmetic graph paper. The stimulus-response curves thus obtained were linear. The effects of mephenesin, 6-methyl-2-amino-benzothiazole, pentobarbital and meprobromate on the stimulus-response curves of both inhibition and facilitation were studied. All of the above mentioned drugs elevated the threshold voltage for inhibition and facilitation. As the animal recovered from the effects of the drug, the stimulus response curves for inhibition and facilitation returned to their original positions. These drugs also altered the slope of both the inhibitory and facilitatory stimulus response curves in that any increment of voltage produced less facilitation and inhibition following the drug. The elevation of thresholds for facilitation by these drugs was greater than the rise in threshold of inhibition; however, with small doses this difference was not striking. These results indicate that ipsilateral inhibition of the patellar reflex is vulnerable to the drugs employed.



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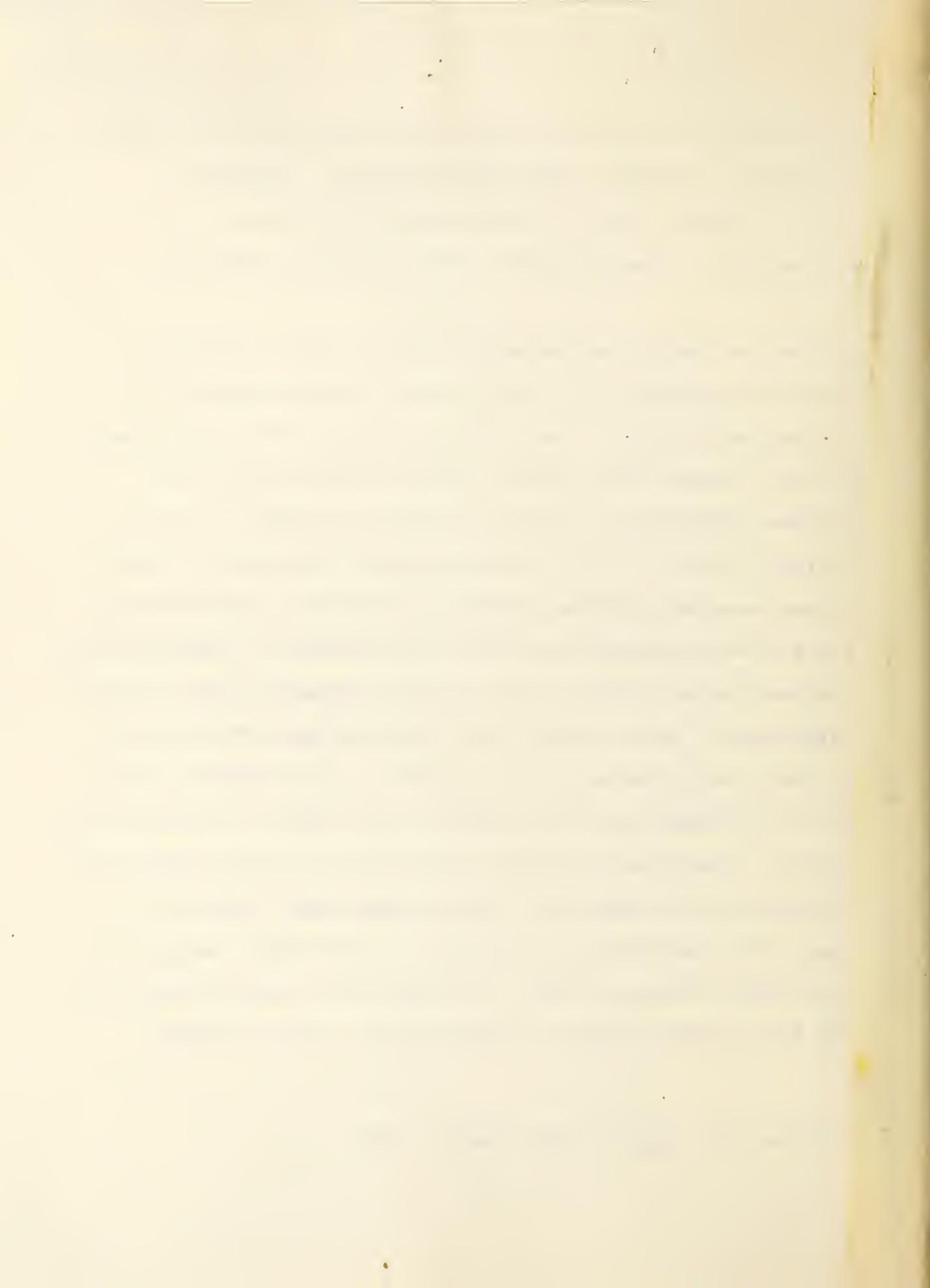
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URINARY EXCRETION OF SHIAA AND CORTICOIDS AFTER MORPHINE, MEPERIDINE,
VALUOPERINE, RESERPINE, AND CHLORPROMAZINE. (ABSTRACT)

H. F. Frazer, Anna J. Eisenman and J. W. Brooks

NIMH Addiction Research Center, PHS, Lexington, Kentucky

Every two weeks, in randomized order, drugs and placebo were administered and urine concurrently collected daily for three consecutive days. The total dosage for three days in mg. (range and average) was morphine sulfate 187-240, av. 226; meperidine 1950-2335, av. 2090; nalorphine 195-225, av. 219; reserpine 4.5-45.0, av. 21; chlorpromazine 1150-1600, av. 1446. Seven men received placebo, morphine, reserpine, and chlorpromazine and 8 men received meperidine and nalorphine. Reserpine and chlorpromazine were given orally, others including saline placebo, subcutaneously. Urine samples were analyzed each 24 hours but only totals for three days are presented. Each patient's total excretion of 5-Hydroxy-3-indoleacetic acid (5HIAA) and 17-hydroxycorticoids, expressed as mg./gm. of creatinine, during three days administration of placebo was used as individual baselines. Changes after each drug were expressed as percentage change from each patient's placebo values. The range and average percentage change from placebo values for 5HIAA were: after morphine,



-12 to -60, av. -19; meperidine, -20 to +34, av. +9; nalorphine, -10 to +31, av. +20; reserpine, +4 to +99, av. +52. Values of SHIAA after chlorpromazine were consistently negative and averaged -57%. This value may be falsely low because of possible interference by metabolites of chlorpromazine. Percentage changes of 17-hydroxycorticoids were: after morphine, -44 to -90, av. -64; meperidine, -52 to +39, av. +2; nalorphine, -18 to -23, av. +5; reserpine, +1 to +63, av. +28; chlorpromazine, -24 to -73, av. -54.

COMPARATIVE CHOLINOMIMETIC EFFECTS OF MONO-,
DI- AND TRI-SUBSTITUTED PYRUVIC ACIDS. H. Busch,
P. V. Nair, M. I. Frank and W. R. Martin. Dept. of
Pharmacology, Univ. of Illinois College of Med., Chicago.

In a previous report (Science, 124: 981, 1956) the cholinomimetic effects of B-substituted derivatives of pyruvic acid were described. The specificity of the type of molecule involved was interesting, inasmuch as pyruvic acid and a series of two-carbon and four-carbon analogues did not show similar effects. In the present studies an effort has been made to synthesize unequivocally mono- and poly-substituted pyruvic acids. Monofluoro- and monochloro-pyruvic acids have been obtained by the hydrolytic cleavage of diethyl fluoro-oxaloacetate and diethyl chloro-oxaloacetate respectively and the monobromo-pyruvic acid by careful and controlled bromination of pyruvic acid. The dichloro- and dibromo-pyruvic acids have been obtained by direct synthesis in which pyruvic acid was treated with sulfonyl chloride or bromine. The monofluoro- and monobromo-pyruvic acids were equipotent in producing salivation and lacrimation and almost twice as potent as the monochloro derivative. Dibromopyruvic acid was twice as potent as the dichloro derivative and four times as potent as the monobromo compound. The derivatives in

order of decreasing potency as analgesics were the dibromo-, monofluoro-, dichloro-, monochloro-, and monobromo-pyruvic acid and in order of decreasing lethality, monobromo-, dibromo-, monofluoro-, monochloro-, and dichloro-pyruvic acid. These data indicate that the dihalogenated pyruvic acids are more potent cholinomimetic and analgesic agents than the monohalogenated compounds. (Supported by grants from the Jane Coffin Childs fund, the National Cancer Institute and U.S.P.H.S. [Cy-2886C].)

action of normorphine in man. R. E. Fraser, M. S. Babb, J. C. L. Johnson, Jr., J. F. Keanan^a and C. D. Van Winkle^b. National Institute of Mental Health, Addiction Research Center, Lexington, Kentucky.

8 mg. of normorphine hydrochloride was given to 8 volunteers and in 10 spontaneously and compared with a similar dosage of morphine sulfate and a placebo in the same subjects. Normorphine caused moderate decreases in respiratory rate, respiratory minute volume, and only slight miosis. These effects were, however, less pronounced. After morphine, these effects were all significantly greater. In another experiment, when every successive doses of 5 or 10 mg. of either normorphine or morphine were compared in the same 8 subjects, above differences were consistently present but not so marked. Action of normorphine is less intense, but longer than morphine. 220 to 330 mg. of normorphine daily substituted effectively for 200 to 300 mg. of morphine for 10 days in 8 patients. The abstinence syndrome developed when 75 to 180 mg. of normorphine was discontinued suddenly after 80 days of addiction in 11 subjects was slow in onset and less severe than that observed after withdrawal of morphine, methadone and cocaine.

Reprinted from THE JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS
Vol. 122, No. 1, January, 1958
Printed in U.S.A.

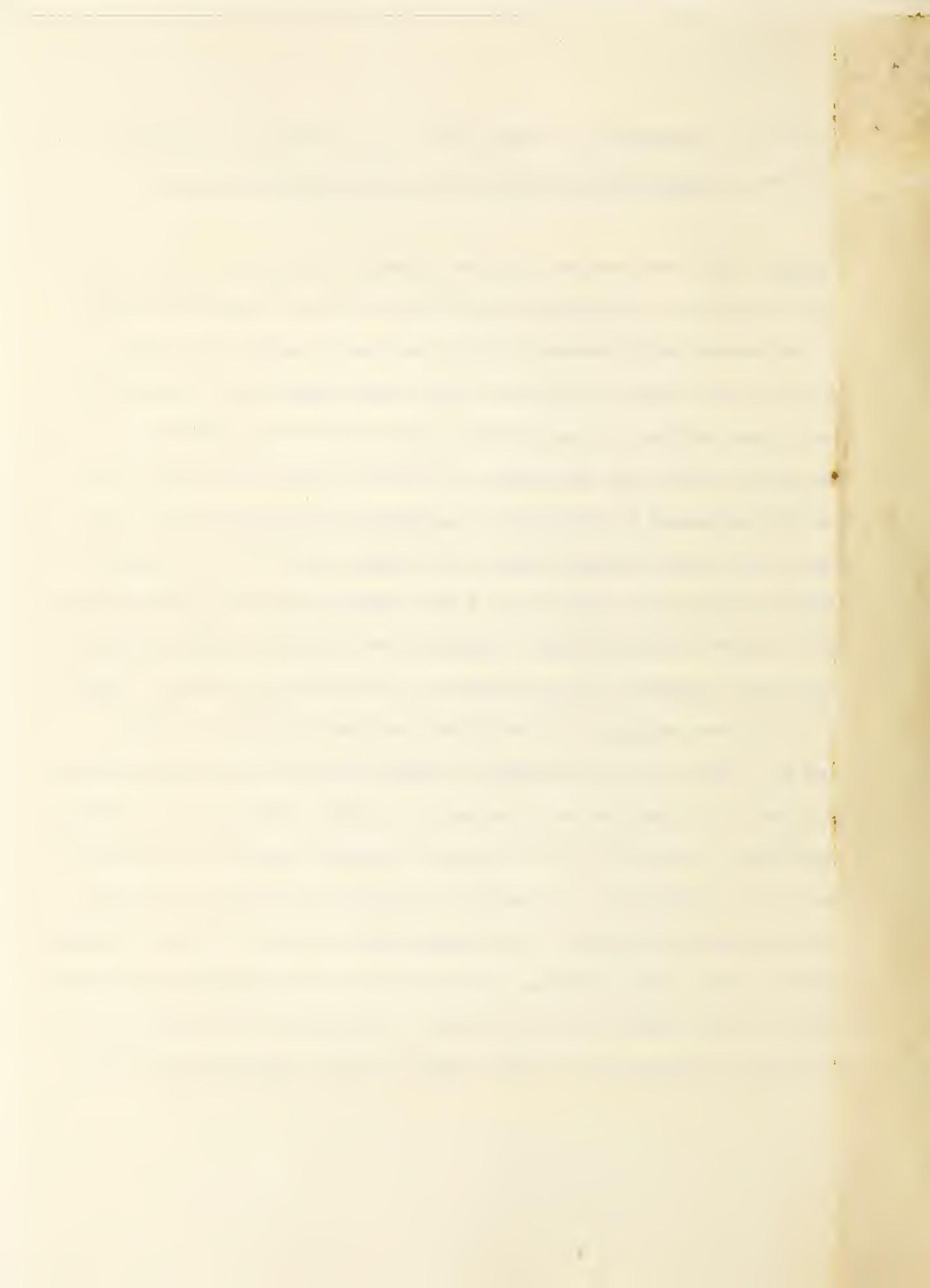
A new method of measuring movement in small animals. M. KNIAZUK, W. R. MARTIN AND K. R. UNNA. *Merck Institute for Therapeutic Research, Merck-Sharpe and Dohme, Rahway, N. J. and Dept. of Pharmacology, Univ. of Illinois College of Med., Chicago.* A crystal oscillator radiating sound into a container of fixed dimension and configuration will require a certain amount of energy to sustain these oscillations. A change (e.g., caused by a moving object) in the amount of energy reflected back to and absorbed from the crystal will cause a change in the amount of energy necessary to sustain the oscillations, and this change can be measured continuously. Upon this principle, an activity cage has been designed. The instrument in its present form consists of a 30,000 cycle/second crystal oscillator radiating sound into a cylindrical plexiglass cage. Slow changes in plate current of the oscillator, which are caused by changes in loading of the crystal, are amplified and activate a relay which in turn activates a counting circuit. Studies of the properties of this cage reveal that although the field strength is not uniform, there are no absolute blind spots. A linear relationship has been found between diameter of a moving object and the number of counts per unit distance of movement. The instrument is capable of detecting the movement of small objects (e.g., $\frac{1}{8}$ inch spheres) and small movements (e.g., respiratory movements of a mouse). The advantages of this activity cage are the absence of blind spots and the ability to detect and count small rapid as well as gross movements. (Supported by grant B-983 from the U.S.P.H.S.)

(7815)



The actions of anticholinics on Renshaw cells. T. R. Martin & V. G. Longo
and L. E. Jones. Dept. of Pharmacology, Univ. of Illinois College of Med.,
Chicago.

Eccles et al. (1954) have brought forth new evidence that direct central inhibition may be mediated by an interneuron and that one type of inhibitory interneuron, the Renshaw cell (Renshaw, 1946), is excited by collaterals of the motor neurons and by certain cholinergic drugs (ACh, physostigmine, nicotine). Experiments were performed in cats lightly anesthetized with pentobarbital. The lumbosacral spinal cord was exposed, the dorsal roots were severed on one side and the homolateral L7 ventral root was stimulated antidromically. Unit potentials were recorded extracellularly from Renshaw cells with micropipettes. The repetitive spikes were counted over 5 msec. intervals and the mean frequency per 5 msec. interval was determined. Elevating the stimulus strength increased the initial peak frequency and the duration of the volley to a maximum. Supraspinal stimuli were employed. As Eccles has previously reported, eserine increased the firing rate and prolonged the bursts, while dihydro-beta-erythroidine decreased the firing rate and shortened the bursts. Nephelinesin was studied in 9 experiments. Doses of 10 to 30 mgm./kgm. produced a small but consistent depression of the firing rate. A transient depression of spike amplitude was observed in several experiments. In two experiments in which a cell was successfully held for over fifteen minutes, a recovery from the depression was observed.
(Supported by grant B-983 from the U.S.P.I.S.) (Presented at the Fall Meeting of the American Pharmacological Society, Baltimore, Md., September 4-7, 1957.)



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Reprinted from FEDERATION PROCEEDINGS
Vol. 17, No. 1 March 1958

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1373. EFFECTS OF ANALGESIC DOSES OF
METHADONE, MEPERIDINE AND MORPHINE
ON PAIN CONDITIONED INHIBITION OF LEVER
PRESSING IN RATS. R. E. Belleville,* F. T.
Pescos, H. E. Hill* and A. Wikler. Natl. Inst.
of Mental Health Addiction Research Ctr., PHS
Hosp., Lexington, Ky.

Rats were trained in a modified Skinner Box to obtain food which was delivered aperiodically around a 1-1/2-min mean. A previously neutral tone, which was terminated with the application of a strong electric shock to the feet, was applied during the test sessions. After training, the tone acquired the function of inhibiting lever pressing to the extent that the rate during the 4-min tone was only 5% of the pretone rate. Experiments were conducted under various drug and placebo conditions; tests were made 75 min after subcutaneous injection of methadone, morphine and placebo, and 30 min following intramuscular injection of meperidine. Since all drugs reduced the rate of lever pressing, the ratio (percentage) of the tone rate to the pretone rate was used as a measure of reduction of inhibition. For each of the drugs, a linear relationship was found between dose and percentage restoration. The following range of effects were found: methadone (0.75-4.50 mg/kg) 20-82%; meperidine (10-25 mg/kg) 30-78%; and morphine (5-9 mg/kg) 49-89% restoration of pretone rate. Methadone was found to be twice as potent as morphine, whereas meperidine was only 1/3 as potent. The potential usefulness of this technique for screening analgesics is being investigated further.

L.S.-LL

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Vol. 17, No. 1 March 1958

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1449. NORCODEINE IN MAN. H. F. Fraser, H. Isbell
and G. D. Van Horn.* Natl. Inst. of Mental Health
Addiction Research Ctr., Lexington, Ky.

Norcodeine hydrochloride (75 mg/80 kg) was given to 9 non-tolerant subjects orally and effects compared in the same subjects with a similar dose of codeine sulfate and a placebo. Mild subjective morphine-like effects, slight miosis, and depression of respiratory minute volume were induced by both drugs. In the same 5 subjects, 5 successive doses (total 290 mg) of norcodeine or codeine given within 36 hr caused no significant effects on rectal temperature, pulse and respiratory rates, blood pressure and respiratory minute volume, but both induced moderate miosis. Norcodeine, when substituted for morphine in morphine addicts, suppressed effectively abstinence symptoms. When the same subjects were addicted to norcodeine and to codeine and attempts made to progressively elevate the dose of each to produce equivalent sedative effects, the dosage of norcodeine attained was about 1/3 that of codeine. The abstinence syndrome in 6 subjects after abrupt discontinuation of norcodeine after 60 days of addiction to 150-500 mg daily was slow in onset, mild, and resembled that observed following withdrawal of normorphine.

EFFECT OF VARIOUS CENTRAL DEPRESSANTS ON PRESSOR RESPONSE EVOKED BY STIMULATION OF THE MESENCEPHALON. W. R. Martin and C. G. Eades (intro. by A. W. Miller). NIMH Addiction Research Center, PHS Hospital, Lexington, Ky.

The effects of chlorpromazine (1 and 4 mgm./kgm.), chlorpromazine sulfoxide (5 and 25 mgm./kgm.), atropine (.2, .8 and 4 mgm./kgm.), morphine (10 and 20 mgm./kgm.), pentobarbital (4 and 8 mgm./kgm.) and ethyl alcohol (1 and 2 cc./kgm.) on vasomotor responses evoked by stimulation of the medial mesencephalon were studied in unanesthetized cats immobilized with succinyl choline. Pentobarbital and ethyl alcohol produced a rise in resting blood pressure in this preparation while chlorpromazine produced a fall. Changes in resting blood pressure were not striking with chlorpromazine sulfoxide, atropine and morphine.

Chlorpromazine, pentobarbital, ethyl alcohol, and to a lesser extent chlorpromazine sulfoxide, produced a decreased reactivity of vasomotor responses to mesencephalic stimulation while atropine and morphine enhanced the response. Morphine and atropine were the only drugs to markedly alter the bradycardia that followed the pressor response. Morphine enhanced this response while atropine abolished it.

the first two years of the experiment. The effect of the vegetation change on the surface energy balance is shown in Fig. 10. The net radiation at the surface decreased by about 10 W m⁻² over the first year of the experiment. This decrease was due to the reduction in albedo caused by the increase in leaf area index. The decrease in net radiation was partially offset by an increase in longwave emission from the surface. The latent heat flux increased by about 10 W m⁻² during the first year of the experiment. The sensible heat flux decreased by about 10 W m⁻² during the first year of the experiment. The decrease in sensible heat flux was due to the reduction in surface temperature caused by the reduction in net radiation. The decrease in sensible heat flux was partially offset by an increase in longwave emission from the surface. The total evapotranspiration increased by about 10 W m⁻² during the first year of the experiment. The increase in total evapotranspiration was due to the increase in latent heat flux and the increase in longwave emission from the surface. The increase in total evapotranspiration was partially offset by the decrease in sensible heat flux.

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PRELIMINARY OBSERVATIONS OF THE URINARY EXCRETION OF
NORMORPHINE AND MORPHINE IN MAN. Jewell W. Sloan, Anna J.
Eisenstein, H. F. Fraser and H. Isbell. NIMH Addiction Research Center,
U.S.P.H.S., Lexington, Ky.

Normorphine (NOR) was determined in the urine of subjects receiving the drug subc. by washing an aliquot at pH 7.2 with 10% isoamyl alcohol in ~~CHCl₃~~, extracting 3 times with 2 volumes 20% ~~isoamyl alcohol in~~ ETC_{1g} at pH 9.4, then with 0.05 N HCl. NOR was estimated after reacting with silico-molybdate reagent. Identification was confirmed by paper chromatography. Morphine was estimated according to Fujimoto et al. (J. Pharmacol. & Exper. Therap. 44: 627, 1954). Within 24 hrs. after injection of 75 or 150 mg. of NOR in 2 subjects, about 75% was found in the urine, of which 55% was unconjugated. Within 24 hrs. after injection of 50-75 mg. morphine in 4 men, about 69% was found in the urine, of which 17% was unconjugated. When urine containing ingested morphine was adjusted to pH 6.2 and incubated with beta-glucuronidase at 37° C. for 65 hrs. yields were similar to those with conc. HCl and heat, but when incubated without enzyme, morphine recovery was the same as for unhydrolyzed urine. With urinary NOR, high increments were obtained merely by incubating at 37° C. at pH 6.2 and the yield was not increased by enzyme, but was in some cases by acid hydrolysis, indicating bound NOR is much less stable than morphine glucuronide.

et l'Inde la fin mai 1971

vers le 1er juillet 1971

vers 25 000 la matinée

vers 100 000 le soir

6350

PHARMACOLOGY AND ADDICTION LIABILITY OF DL- AND
D-PROPOXYPHENE (DARVUN). H. F. Fraser and Harris
Tsbell, NIMH Addiction Research Center, Lexington,
Kentucky.

Single doses of dl ranging from 50 to 1000 mg orally, or of d-propoxyphene ranging from 50 to 650 mg orally or 5 to 60 mg subcutaneously did not induce a full pattern of morphine-like effects. When substituted for morphine for either 24 hrs. or 14 days in addicted patients both dl and d partially suppressed symptoms of abstinence from morphine but they were much less effective than codeine. Two of 5 patients who received dl chronically withdrew from the experiment; 3 patients continued after the daily dosage was reduced from 1200 to 700-850 mg daily; all patients disliked the drug because of its disagreeable side effects; 10 mg of nalorphine did not precipitate definite abstinence; following withdrawal of dl only minimal abstinence was observed. Five patients were addicted to d-propoxyphene for 53 days, and although liking the effects of the medicine initially they later developed a progressive distaste for it. After withdrawal of d-only minimal signs of abstinence were observed. Concluded that addiction liabilities of both are substantially less than that of codeine.



A small number of new antibiotic substances can be introduced into the market if additional pharmacokinetic data are available.

REFERENCES

1. The effects of glucose administration upon human basal plasma insulin levels from one administration to 10. J. and T. J. and W. G. Johnson. *Endocrinology* 68: 1000-1004 (1961).
2. The influence of insulin levels and glycemia. And the influence of glucose on strength and memory. Glucose was administered in 5% concentration by addition to the liquid of three measures. 2 mg of insulin were injected by syringes. 1 g 20% D-glucose. After one injection, the additional insulin resulting produced by injection, did not have insulin sugar and glycemic was very considerably different for substances added to the two drugs. Sugar substance were extremely modified in one another substances from administration to 10. *Mémoires Académie Belge* 75: 195 and *Proceedings* 1950 they used a short (18 days) extension period. During this extension cycle, subjects took their insulin and glucose as usual with a high degree of accuracy. 50% covering minutes and disclosed a preference for insulin. The only significant difference to effect, however in the subjects between low HbA_{1c} group was a slight increase of insulin on the endocrine and metabolic following injection. There was a tendency but incapable to produce a more pronounced difference between than insulin and high extension to show a higher degree of vulnerability to metabolic changes. Thus the results come and when I may add that this study were conducted on a single individual.

One year old the day of separation

in 1977 joined by more 200000 young adults who had left their
militant communities in 1976 and 1977. By now many have

THOMAS

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FRIEDMAN, B. S.: Monitoring Opiate Addiction in the Ambulatory Setting.

2000 AMERICAN MEDICAL ASSOCIATION ANNUAL MEETING ON MORPHINE
AND RELATED ANALGESICS

The Neurologist, 12 (2) 27 (Fall 1965).

1. Experiments were conducted to quantitate the attitude of opiate addicts toward cocaine or cocaine-sin in doses previously administered in single and continuous dosage schedules. Studies employing Single and Continual Dosage Attitude Questionnaires using independent patients and observers ratings indicated that no preference existed of opiate addicts for various morphine-like drugs. In the experimental setting tested, cocaine well with the longer time stability of morphine.
2. A "short" cross-tolerance double blind drug substitution procedure of 15-30 minutes was found to be satisfactory for developing significant degrees of physical dependence in the rats of poison control live drugs, but additional studies are necessary to determine the possibility for predicting the degree of physical dependence induced by each drug.

NSUS Addiction Research Center
P.O. Box 12000, KR 90000

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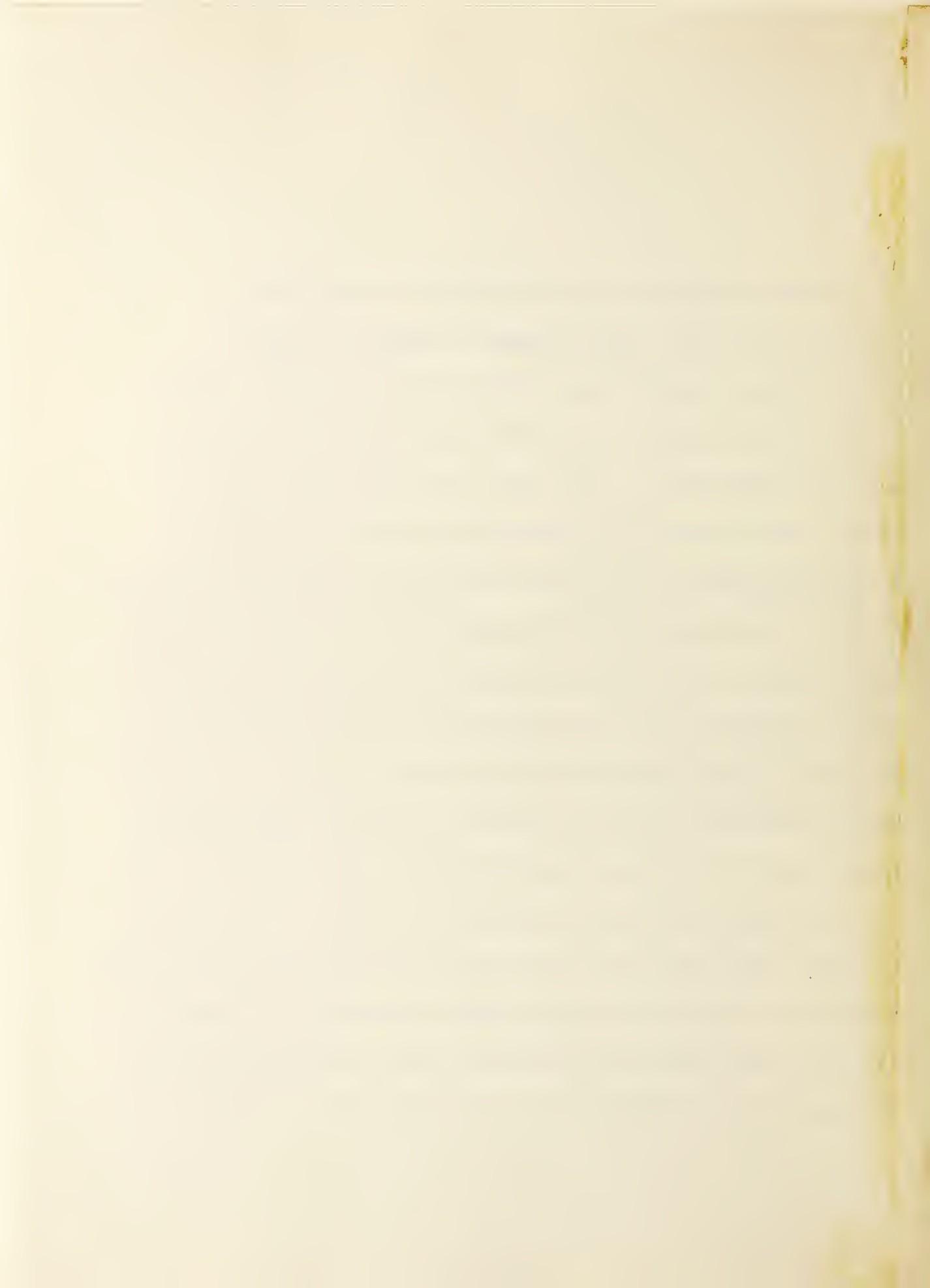
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-PROGRESSIVE INCREASE OF ELECTROSHOCK CONVULSIVE
THRESHOLD IN CATS. Carl F. Essig and Harold G. Flanary.*

KMSE Addiction Research Center, USPHS Hospital, Lexington, Kentucky

The currents necessary to reproduce human electroconvulsions (ECS) increases (Milnerovsky, L., *Rev. Phys. Acc. Nerv. Ment. Dis.*, 26: 175, 1949). Beyond aspects of this phenomenon in cats are reported herein. An insulated platinum electrode was fixed in the skull over each hemisphere. A Cossor 5-4 stimulator was used to deliver current in 3-volt increments every 5 minutes until a convolution occurred at threshold. Two msec biphasic pulses at 100/sec were delivered for 5 seconds. Current was determined by using the IR drop across a 100-ohm resistor. Three cats were convulsed 95 to 133 times during 48 to 155 days. Initial thresholds varied from 5.0 to 8.0 and eventually increased to levels between 9.0 and 13.7 milliamperes representing elevations of 44 to 46%. Thresholds fell to original levels within one to five weeks of discontinuing daily stimulation. Spontaneous convulsions developed in one cat after having 142 electrical seizures; a phenomenon which disappeared when stimulation was stopped. Histological studies indicate the same minor alterations in cerebral cortex.



Federation Proceedings, 19; (1) 281 (March) 1960.





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The effects of standard subcutaneous doses of morphine sulfate (20 mg/kg), salicylates (ECI 20 mg/kg) and intravenously infused morphine (20 mg/kg/hr) were studied on pulse rate, respiratory rate, rectal temperature, capillary oxygenator, skin color, reflexes, abdominal, ocular, nasal, mouth, pharyngeal, laryngeal and respiratory reflexes. During an 8-hour infusion of morphine behavioral depression, pupillary constriction and depression of the skin twitch and withdrawal reflexes were maximal after 2 hours of infusion and became less intense thereafter. A standard dose of morphine administered 27 hours after the end of infusion was less effective than a pre-infusion standard dose in producing miosis, behavioral depression and depression of skin twitch and withdrawal reflexes. Tolerance to morphine was evident during behavior and was demonstrable 17 hours after infusion. In another series of experiments morphine (20 mg/kg) was administered immediately after a 2-hour infusion and produced the following signs and symptoms: violent tremors, salivation, rhinorrhea, lacrimation, vomiting, nystagmus, decerebration, mydriasis, marked tachycardia and hypertension. These signs appeared within 5 min after injection of morphine after infusing salicylates (5 g/m, and slowly increased thereafter, being completely disappears by 30 min.

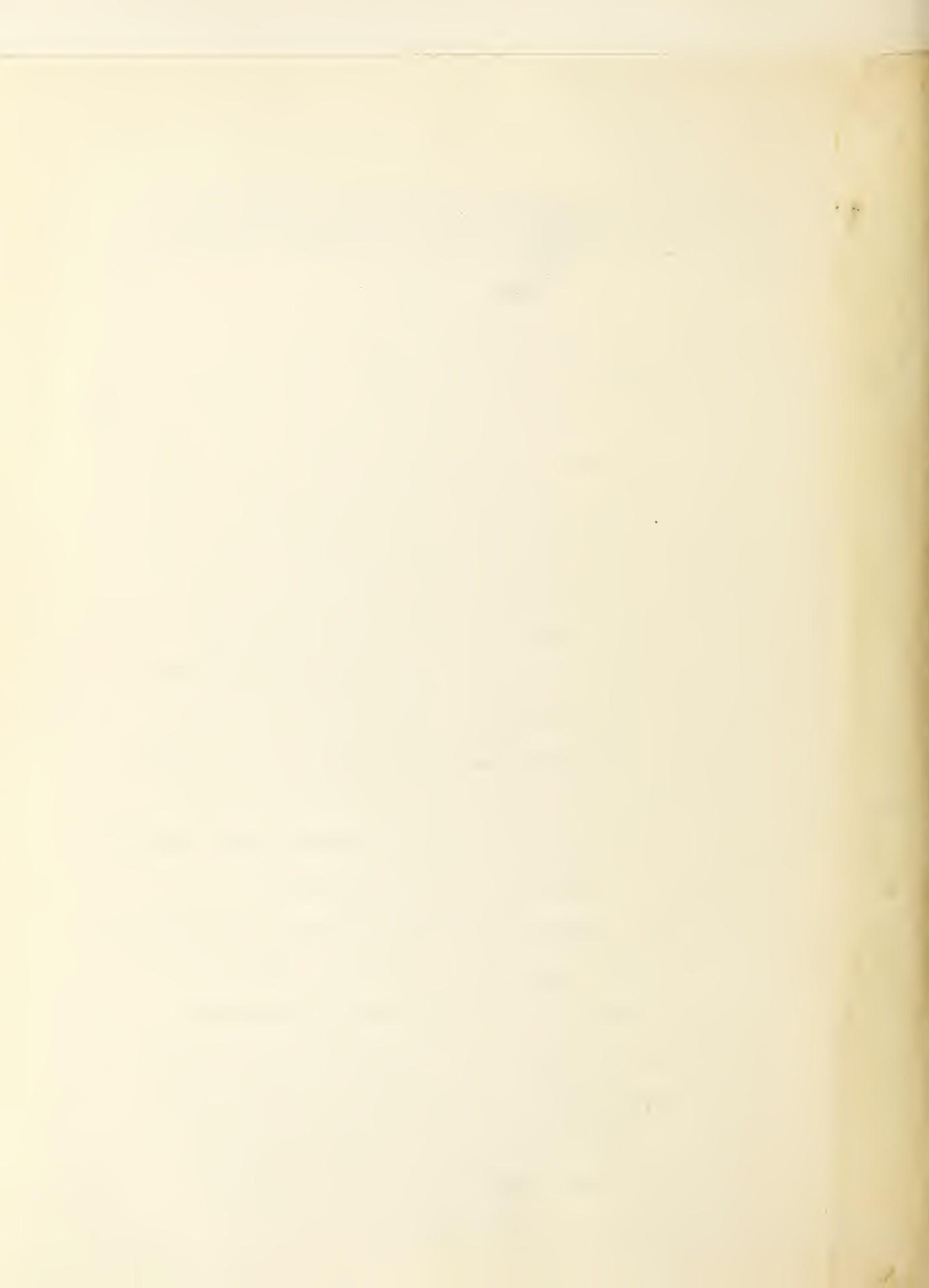


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and the following table gives the approximate effect of morphine on the respiratory rate and blood CO₂ tension in addition to the results obtained by Lusk and Dill (1922).

All experiments were performed on healthy volunteers. Acetaminophen was given to masking a morphine analgesic reaction at recommended doses. Several blood collection times after acetaminophen were taken, and were determined on the unopacified serum. Morphine sulfate (10 to 20 mg/kg) markedly depresses respiratory rate (20 to 9/min), elevated serum CO₂ (39 to 42 ml/100 ml) and depresses serum pH (7.69 to 7.54). Morphine (25 mg/kg) strongly accelerated respiratory rate (11 to 30/min), decreased serum CO₂ (38 to 34 ml/100 ml) but did not significantly affect serum pH (7.69 to 7.67). When acetaminophen (5 mg/kg) was administered after morphine a marked increase in respiratory rate occurred (9 to 32/min) which slowly decreased, stabilizing at a value slightly above control level (103 ± 20/min). Serum CO₂ levels and pH were respectively low and higher than control values (33 ml/100 ml and 7.69) at a time when respiratory rate had stabilized. On the basis of these findings it is suggested that morphine depresses the homeostatic level and creates a state in which the equilibrium concentration of serum CO₂ is higher than the control value. Administration of acetaminophen rapidly shifts the homeostatic level (sensitivity to CO₂) back to an above control position producing a marked tachypnoea.



LIVERED ANIMALS AND DISORDERS LEVELS IN ANIMALS OF MORPHINE
AND SALINE FOLLOWING ACUTE WITHDRAWAL (ABSTRACT). J. Sloan*,
J. T. Zimmerman, J. W. Broder*, and J.R. Martin. NIMH Addiction
Research Center, PGH Hospital, Lexington, Ky.

The brain, heart and spleen of rats treated with progressively increasing doses of morphine (10 to 320 mg/kg/day over 10 days) or normal saline were analysed spectrophotometrically for catechol amines (CA) and serotonin (S) content 24, 48 and 72 hours following abrupt discontinuance of injections. During the induction cycles, control animals gained weight whereas the weight of animals receiving morphine remained approximately constant. On termination of all injections, morphine addicted rats lost weight during the first 48 hours, while saline treated controls continued to gain. The weight of the spleen and heart of addicted animals was less than that of saline controls. No statistically significant differences in either brain CA or S levels were found between rats withdrawn from morphine and saline controls. Heart CA levels of morphine addicted rats, when calculated on a mcg/gm basis, were slightly lower than saline controls 24 hours after withdrawal and significantly lower at 48 hours. When heart CA content was calculated on the basis of mcg/heart, the drop was highly significant at 24 and 48 hours. Splenic CA and S levels, calculated on the basis of mcg/gm, were significantly elevated 24 and 48 hours post injection, but there were no significant differences in splenic CA or S when the levels were calculated on the basis of mcg/spleen.

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A COMPARISON OF THE EFFECTS OF INTRAMUSCULARLY ADMINISTERED PENTOBARBITAL SODIUM AND MORPHINE SULFATE IN MAN. W. R. Martin, H. F. Fraser and N. Isbell. NIMH Addiction Research Center, FMS Hospital, Lexington, Ky.

The effects of graded doses of pentobarbital (P)(150, 200 and 250 mg) and morphine (M) (8, 16 and 32 mg) were studied on pupillary diameter, post-rotatory nystagmus (PRN) and responses to single- and chronic-dose questionnaires (Fraser et al., J. Pharm. exp. Therap. 133: 371, 1961) in 12 male subjects. P, at all dose levels, was identified as such by 75% or more of the subjects. Only 25% of the subjects identified M at the 8-mg dose level, whereas 75% identified the 32-mg dose level as M. M was most commonly mistakenly identified as a barbiturate, and, conversely, P was most commonly mistaken as an opiate. Contributing to the confusion of M and P by subjects is the fact that both drugs produced many similar signs and symptoms such as miosis, PRN, scratching, conjunctival injection, sedation and sleep. However, only miosis and scratching were strongly and positively correlated with dose level for M, and only PRN, sleep, and drunkenness for dose levels of P. In addition to the above mentioned parameters, allowing differentiation between M and P, the subjects' liking for M was positively correlated with increasing dose levels, but negatively correlated with increasing doses of P.

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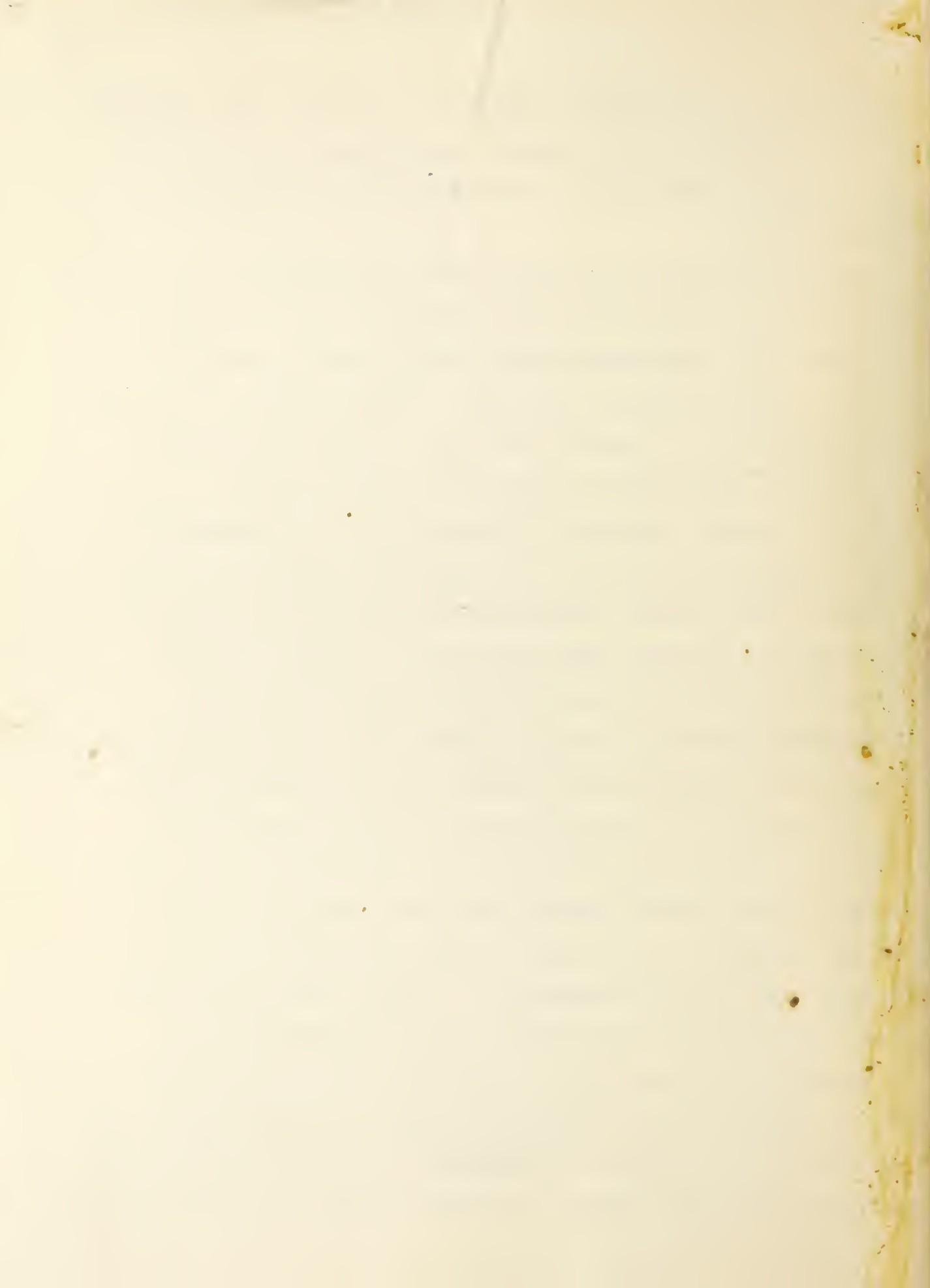
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EVALUATION OF A PHOTOGRAPHIC METHOD OF ESTIMATING PUPIL DIAMETER
IN MAN (ABSTRACT). S. S. Jones, W. R. Martin, H. Isbell and
D. F. Fraser. NIMH Addiction Research Center, PHS Hospital,
Bethesda, MD.

Statistical analysis of three experiments was done to determine the sources of variation and the reliability of estimating pupil diameter. Two experiments used a Graphic camera equipped with an f 2.8 lens and a Polaroid Land back. Polaroid 3000 film and low illumination (5 ft. candles) were used. The first study had 12 subjects, photographed twice at 30 minute intervals, once each week for 7 weeks. Because of differences in illumination due to small changes in position of the regulating lightmeter a second study was done, using 5 subjects photographed three times at 15-30 minute intervals once each week for 6 weeks, in which lightmeter position was controlled and two observers made independent measures of pupil diameter. The results of the two studies were compared with replicate control measures obtained in 22 subjects at 3 weekly intervals, using the photographic method of Fraser *et al.* (J. Pharmacol. exper. Therap. 105: 459, 1958). In addition to highly significant individual differences in pupil diameter, there was a tendency for pupil diameter to decrease on repeated measurements. Absolute differences in mean and their standard errors between repeated measures for the 3 studies were respectively: $.18 \pm .02$, $.28 \pm .03$, and $.35 \pm .04$. It is noteworthy that differences between successive measures in excess of 1.0 mm occurred occasionally. The correlation between pupil diameter and illumination levels observed was less than .05.



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TODAY, APRIL 10, 1952.

Author, Mr. (LAWRENCE M. STONE, JR., *in press*) demonstrated
some difference between the two substances in iron. Nevertheless
the two substances have the same carbon-carbon structural and
physicochemical properties. The above results stimulate
the consideration of clinical and cross tolerance with 150
mg. dinitrophenol. The results will also indicate
if a one-year delay in this case subject received either
one drug or either periods of chronic administration
and subsequent "conditioned" the direct tolerance of the
body to the drug by not being receiving, and "conditioned"
the body tolerance to the 150 mg. with the alternate drug.
The author was beginning with control drug observation
remained for each subject having nonballistic portions
of their histories investigated by the investigator and made
known to him as to the psychosomatic, hyperthyroidism,
and changes of hemostatic function. Cross tolerance
was measured between 150 mg. dinitrophenol and

8622

EFFECTS OF ADDICTION TO I.V. HEROIN AS COMPARED TO PLACEBO ON PATTERNS OF ACTIVITY. H. F. Fraser, B.E. Jones,
D.F. Rosenberg and A. K. Thompson. NIMH Addiction Research Center, PHS Hospital, Lexington, Ky.

In a double-blind study 5 nontolerant prisoner heroin addict volunteers received 4 intravenous injections daily. Each subject was indoctrinated without medication for 7 days, then a placebo was given for 30 days, followed by i.v. heroin which started with 10 mg daily and increased to an average of 95 mg daily by the 18th day and was maintained at that level for 42 more days. Average hours lying horizontal on bed daily while on placebo were 9.96; during first 3 days on heroin, were 9.16; during last 57 days on heroin, 12.47. Hours of sleep for above respective regimens were 6.89, 5.81 and 8.11. Hours off ward daily were respectively 3.34, 5.06 and 2.41. Pedometer miles daily were respectively 5.24, 5.02 and 4.51. Observations indicate that initially heroin increased "activity" but later significantly depressed it. Pursuit rotor performance conducted under no particular motivation (patients not advised of score) declined slightly after heroin was started but improved thereafter, indicating that the

depressant effects of heroin, exhibited chronically, were not due to psychomotor impairment. The experiment also demonstrated (1) satisfactory correlations between various activity measurements, and (2) distinctly different patterns of activity on days Monday through Friday as compared with Saturday and Sunday.

The Pharmacologist, 4: (2) 154, 1962.

8935

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FACTORS REGULATING ORAL CONSUMPTION OF ETONITAZENE SOLUTION IN MORPHINE-
ADDICTED RATS. A. Wikler, W. R. Martin, F. T. Pescos and C. G. Eades*.
NIMH Addiction Research Center, USPHS Hospital, Lexington, Ky.

Experimental rats stabilized on morphine (MS) 200 mg/kg given i.p. at 0730 daily (E's) drank less H₂O from 1500 to 0800 next morning than non-addicted controls (C's), though total for 24 hrs was not different. In contrast E's drank significantly more than C's when etonitazene (ETZ) in .005 or .01 mg/ml aqueous solution was substituted for H₂O in E's, and the same volumes as C's when ETZ concentrations (E's) were .02 or .04 mg/ml. In E's, total amounts of ETZ consumed were .629, 1.157, 1.739 and 3.055 mg/kg with increasing order of concentration. Drinking all concentrations of ETZ suppressed "wet dogs" and hypothermia (MS abstinence signs) in E's. After drinking ETZ, .01 or .02 mg/ml for 17 hrs, E's did not differ from C's, but showed decreased activity when ETZ was .005 mg/ml and increased O₂ consumption rate (OCR) and colonic temperature (CT) when ETZ was .04 mg/ml. Substitution of ETZ (.075 or .165 mg/kg) i.p. for MS (200 mg/kg) i.p. did not alter diurnal patterns of H₂O drinking in E's, and like MS, suppressed MS abstinence signs and increased activity, OCR and CT. In normal rats, fluid consumption was not changed by substitution of ETZ (.005 or .01 mg/ml) for H₂O from 1500 to 0800 but activity was decreased and 1 of 4 rats died on ETZ, .01 mg/ml. In normal rats, MS (30 mg/kg) i.p. decreased activity and elevated CT; ETZ (.075 mg/kg) i.p. decreased activity and increased OCR and CT. The primary factor regulating consumption of ETZ solution in MS-addicted rats appears to be suppression of MS abstinence phenomena.

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TOLERANCE AND PHYSICAL DEPENDENCE TO MORPHINE IN RATS.
W. F. Martin, A. Wikler, C. G. Eades and F. T. Pescor
NIMH Addiction Research Center, PHS Hospital, Lexington,
Ky.

The effects of morphine sulfate (MS) in non-tolerant and tolerant Wistar strain rats and the effects of abrupt withdrawal of MS in MS-addicted rats (320 mg/kg/day) were studied on body temperature, metabolic rate, body weight, "activity", respiratory rate, water consumption and "wet dog" phenomenon (spontaneous skin twitches, Wikler et al., Fed. Proc. 19: 22, 1960). MS (100 mg/kg) produced cyanosis and a decrease in "activity" in non-tolerant rats and an increase in body temperature, metabolic rate and "activity" in tolerant rats. Abrupt withdrawal of MS in tolerant rats produced two distinct syndromes: a primary syndrome which appeared 8-12 hours after the last dose of MS, achieved maximum intensity by 24 hours, persisted for 72 hours and was characterized by the appearance of "wet dogs", irritability, weight loss, increased activity and the return of body temperature and metabolic rate to normal or subnormal levels. A secondary syndrome was manifest by the 4th day after the last dose, persisted for over 2 months and consisted of a significant increase in metabolic rate, body temperature and water intake.

It is concluded that abrupt withdrawal of morphine after chronic intoxication of the rat is followed by an abstinence syndrome lasting approximately 3 days; however, post-addicted rats differ from non-addicted control rats for over 2 months.

The Pharmacologist, 4: (2) 154, 1962.

Effect* of Morphine and Pentobarbital on Electrodermal Activity and Conditioned Electrodermal Responses in Man. B.E. Jones*, H.F. Flanary* and T.H. Clements*, NIMH Addiction Research Center, PHS Hospital, Lexington, Ky.

In a double-blind study 64 subjects (Ss) received intramuscularly either morphine sulphate (MS), 8 or 16 mg/70kg, pentobarbital sodium (PS) 200 mg/70kg, or saline placebo (SL) 1cc/70kg. Half of the 16 Ss (conditioning group) in each drug group were presented with .5 sec. tones (1000 cps; 70 db.) paired with .5 sec. electric shocks (500 cps; 40 vdc). The other half of each drug group (conditioning control group) received equal numbers of tones and shocks without pairing. All Ss received 4 non-paired shocks and tones before either the conditioning or conditioning control procedures, and 7 tones after conditioning or control procedures. Electrodermograms (EDG) were obtained for all Ss. In a second study, EDGs were obtained repeatedly on 10 Ss during presentation of tones and a loud bell at 10 minute intervals, under the same drug conditions used in first study. Among Ss receiving shocks, MS 16 significantly reduced the rise in basal skin conductance (tonic EDG) seen in PS and SL Ss, but did not impair responses to discrete shock or tone (phasic EDG). MS 16 moderately reduced, and PS markedly reduced EDG conditioned responses. Among Ss not receiving shock the tonic EDG of the MS 8 and 16 conditions did not differ from the SL condition. Results indicate that MS has greater effect on tonic than on phasic EDG, but only among Ss receiving shock.

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URINARY EXCRETION OF CATECHOLAMINES AND SOME OF THEIR METABOLITES DURING A COURSE OF MORPHINE ADDICTION AND WITHDRAWAL IN TWO HUMAN SUBJECTS. H. Weil-Malherbe, E.P. B. Smith, A. J. Eisenman and H. F. Fraser. NIH, Saint Elizabeths Hosp., Wash., D.C. and Addiction Research Center, Lexington, Kentucky.

The excretion of catecholamines (epinephrine, norepinephrine and dopamine) and of some metabolites (metanephrine, normetanephrine, 3-methoxy-4-hydroxy-mandelic, 3,4-dihydroxymandelic and 3,4-dihydrophenylacetic acids) has been determined in two volunteers who, after a preliminary observation period of 30 days, received increasing doses of morphine sulfate s.c., reaching a maximum of 250 mg/day after 17 days. This level was maintained for a further 81 days in subject 1 and 20 days in subject 2. Observations were continued during a withdrawal period (7 days) and recovery period (case 1: 22 days, case 2: 60 days).

The excretion of most metabolites was increased during the incremental as well as the plateau phase of addiction in both subjects. In subject 1 norepinephrine excretion and in subject 2 epinephrine excretion was increased during the incremental phase; dopamine excretion was increased in both subjects.

Contrary to expectation, the excretion data did not indicate any significant sympatho-adrenal activation during the withdrawal phase.

Fed. Proc., 22: (C1 (Pt. 1) 567 (Mar.-Apr.) 1963.

the 2000th term of the sequence of the first column
of the matrix M_{n+1} is approximately equal to $(\ln n)^{1/(n+1)}$.

It follows that $\lim_{n \rightarrow \infty} (\ln n)^{1/(n+1)} = 1$.

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